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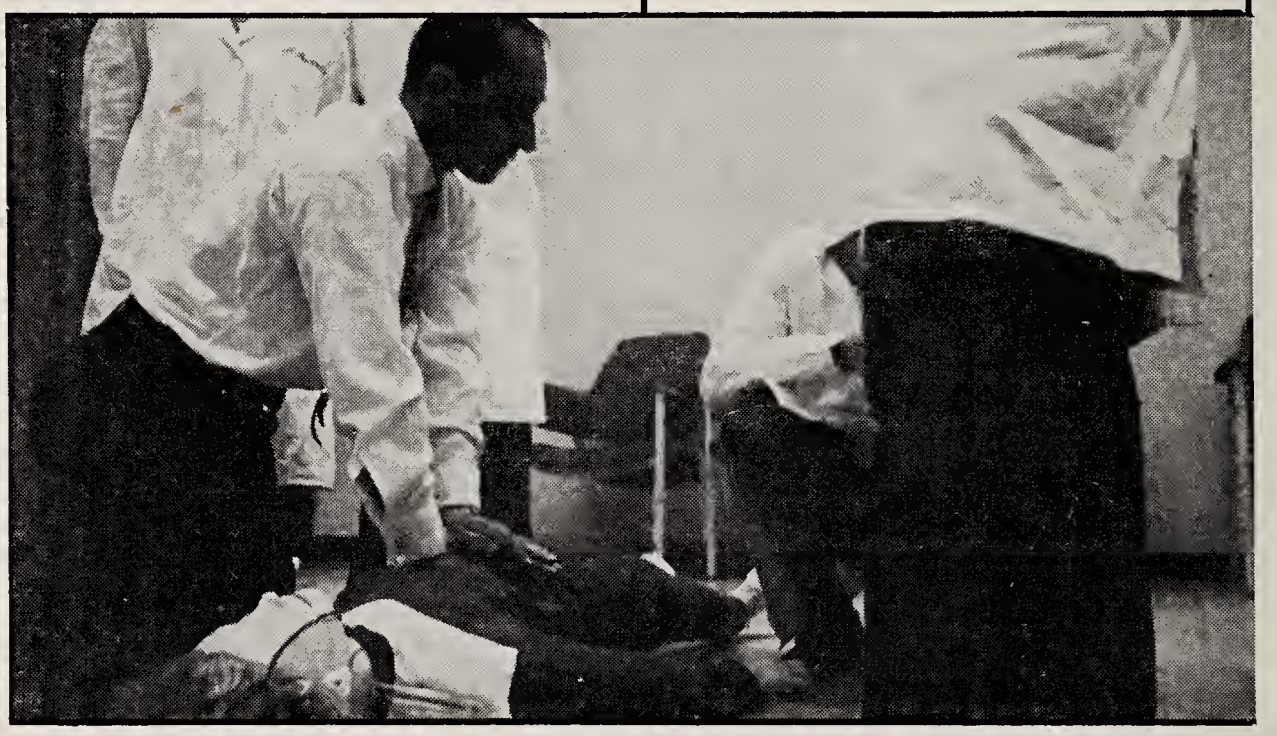

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Editorial

When pathological processes involve the pancreas, the presenting symptomatology can be quite varied due to the anatomical position, the nerve supply, and the exocrine and endocrine functions of the gland. There may be involvement of the common bile duct, the portal circulation, or the lung and pleural cavity on the left side because of their proximity to the pancreas. Abdominal and back pain can be produced by both visceral and somatic nerve involvement. Disturbances of the exocrine functions of the gland can produce electrolyte abnormalities and malabsorption states. Abnormalities of the metabolism of glucose can result from disturbances of the endocrine functions of the pancreas. Symptoms may also be produced which do not suggest an organic source for a long time; and it is not uncommon to find that neurosis is the clinical explanation for the problem for months prior to the diagnosis of chronic pancreatitis. Both symptomatology and investigation will be dealt with in greater detail in the articles contained in this issue.

To the clinician, the pancreas is characterized mainly by inapproachability. Anatomically it is not only smaller and more deeply located than any other major part of the gastrointestinal tract, but it is also obscured in its physical configuration by fat and peritoneal packing. When normal, it cannot be seen, felt, or heard. It cannot be made radiopaque, and it has enough physiological reserve so that it exhibits no evidence of deficiency until disease is far advanced. For these reasons, pancreatic disease is more difficult to diagnose than most. In this issue, we have tried to present an interesting and informative selection of pancreatic pathology.

S. K. B.

Acute Haemorrhagic Pancreatitis

John E. Kensora, M.D.

Acute pancreatitis refers to a diffuse inflammation of the pancreas which is characterized clinically by the abrupt onset of agonizing epigastric pain. The pain radiates to the back, the shoulders or along either rib margin. There is marked epigastric tenderness and moderate rigidity accompanied by nausea and vomiting. Characteristically profound shock and advnamic ileus are present.

The diagnosis of acute pancreatitis is made in between 1/500 and 1/600 admissions to the Boston City Hospital, but the incidence is much less than this at the Toronto General Hospital.

The disease may occur at any age, but is more common in obese middle aged individuals. Commonly the patient is an alcoholic or has gallbladder disease. An attack of pancreatitis may follow abdominal surgery near the gland or blunt abdominal trauma. Other conditions with which pancreatitis may be associated are hyperparathyroidism, hyperlipemia and hypercholesterolemia. The disease has also been reported as a familial trait.

A simple classification describes the forms which the disease may take. The disease is either acute or chronic. In the acute form, the attacks range in severity from mild, through moderate, to severe. A particular attack may begin and remain mild, or progress rapidly to the severe type. On the other hand, the disease process may be so severe that the gland is destroyed and the patient dies within one-half hour of the onset. Relapsing pancreatitis refers to recurrent episodes of acute pancreatitis Chronic pancreatitis is the outcome of the acute forms whereby the gland atrophies and its secretions become deficient.

PATHOLOGY OF PANCREATITIS[8 15 16]

Macroscopically, a mild attack leaves the gland swollen with a few tiny haemorrhagic areas scattered about. Microscopically a mild pancreatitis is characterized by interstitial oedema. If the lesion progresses, red blood cells and fibrin clots are seen in the interstitium, but the stroma remain swell preserved in the early phases. Small areas of focal necrosis of endocrine and exocrine cells are found. Neurtrophils infiltrate the margins of the necrotic areas. When the disease becomes severe the gland becomes very swollen and infarcted, and portions or all of it may be converted into a mass of clot.

Focal areas of fat necrosis occur in stomal peripancreatic and abdominal fat deposits. Vacuolated fat cells become transformed into shadowy outlines of cell membranes filled with pink granular material thought to be insoluble calcium soap. In most cases the peritoneum contains a serous turbid brown tinged fluid in which oil globules can be found. Fat necrosis can occur anywhere fat is found in the abdomen and occasionally outside the abdomen, for example in the pleural spaces. This is probably due to absorption of lipase into the blood and lymphatics surrounding the pancreatic tissues.

PATHOGENESIS

The exact cause of pancreatitis is unknown, however several theories have emerged in an attempt to explain the pathological processes. These are as follows:

(1) The Common Channel Theory.
(2) Obstruction of the Pancreatic Duct(s).
(3) Autocatalytic Activation of Trypsinogen.
(4) Parenchymal Ischaemia.
(5) Allergy.
(6) Autoimmunity.
(7) Duodenal Reflux.

I will discuss each of these theories in turn.

1. The Common Channel Theory

At the turn of this century, Opie discovered a stone impacted at the lower end of the common bile duct of a patient dying of acute pancreatitis. He felt that this obstruction caused reflux of bile into the pancreatic duct thereby activating enzymes intraductally. These active enzymes would cause necrosis of ducts and consequent destruction of the gland. Thus the common channel theory was born since that time, this theory has become much more elaborate. For example, if there were an obstruction to the lower end of the common bile duct and the gall bladder were stimulated to contract, bile would be forced ito the pancreatic ducts. Here, bile salts would activate trypsinogen, chymotrypsinogen and carboxypeptidasinogen to their active forms. The force of the gall bladder contraction would rupture some tiny ducts thereby releasing the active enzymes to destroy the gland.

Several pieces of evidence have accumulated which tend to detract from this theory.

The first,[6] is that a common channel or anatomical connection between pancreatic and bile ducts is present in only a few patients with pancreatitis. In the general population a common channel is present in between 30 and 70% of people.

A second important factor is that bile does not activate pancreatic enzymes.

Third, an obstruction to the lower end of the common bile duct is rarely found in patients with pancreatitis even in patients with a common channel. Supporters of Opie say that possibly, the obstruction in these cases is due to spasm of the sphincter of Oddi. Caroli points out, however, that if the sphincter is spastic both the common bile duct and the pancreatic duct are blocked thereby preventing any sort of reflux.

One fact in favour of this theory is that one of the most effective ways of producing experimental pancreatitis involves trying off the pancreatic ducts distally and infusing them with a mixture of bile and trypsin.

A further point is that although bile cannot activate enzyme precursors, it can potentiate the action of any active pancreatic enzyme. As well, bile is a cytolytic agent and is capable of destroying acinar cells, thereby releasing their contents. One intracellular enzyme, cytokinase, is capable of activating trypsinogen. Thus bile can indirectly activate pancreatic enzyme precursors.

2. Pancreatic Duct Obstruction

I do not intend to dwell for long on the topic of pancreatic duct obstruction. This never happens. Banting and Best in their early experiment on diabetes, tied off the pancreatic ducts of animals to induce secondary pressure atrophy of the exocrine portion of the gland. Clinical experience, moreover, reveals that tying off of both major and minor pancreatic ducts helps cure some people with the acute disease.

3. Auto-activation of Tripsinogen

The auto-catalytic activation of trysinogen is a very refined theory of recent development. Normally a low level of active trysin is found in the blood. This circulating enzyme is normally inhibited by polypeptides found in the serum and organs such as pancreas, parotid glands, liver, spleen and lungs. (Werle A52). If either the amount of circulating trypsin were slightly increased or the amount of inhibitor were decreased, this circulating enzyme by means of 'auto-catalysis' is capable of converting glandular trypsinogen to trypsin. Perhaps such a condition could be produced if pressures within the pancreatic ducts were raised sufficiently to rupture some of the finer ductules. A chain reaction would then be set up. High serum levels of trypsin would convert intra-ductal and glandular precursors to more trypsin and chymotrpsin which would then destroy acinar cells thereby releasing more precursor enzymes and so on. This particular theory is difficult to prove wrong or to verify. It is known, however that trypsin itself can covert trypsinogen to trypsin both in vitro and in vivo. Trypsin can also convert chymotrypsinogen to chymotrypsin. This theory might explain the work of Stein, Powers and Browne (56) who produced acute hemorrhagic pancreatitis by infusing trypsin into the pancreatico-duo-denal artery of animals.

Although not much work has been done in regard to the theory of auto-catalysis of trypsinogen, much time and effort has been spent investigating the effects of active trypsin itself on the pancreas.

Some workers have been able to reproduce acute pancreatitis regularly by infusing the gland with trypsin; and others, using similar methods, have failed.

Mathews and McPhedren,[1] confused by the varied reports of experiments with trypsin, decided to investigate the problem themselves. Massive doses of active trysin were administered to dogs in a variety of ways. They infused the duct system of the pancreas of some animals and injected the parenchyma of the glands of others some of whom had their pancreatic ducts tied off. In this series no lethal acute pancreatitis occurred. In 40% the gland was normal, in 60% there was mild pancreatic fibrosis in the interlobular spaces. They concluded that trypsin itself did not damage pancreatic cells nor initiate the process of pancreatitis. This experiment verified the work of Anderson; Elliot; and Henderson.

These findings however, were to be expected. Werle and Forell[10] in a paper in 1959 stated "native non-denatured proteins are very resistant to attack by enzymes. This fact may explain our observations that even infiltrative injection of active trysin into the pancreas of the rat did not kill the animal. For the pancreatic protein to become vulnerable to proteolytic enzymes there must be organic damage in addition to the activation of trypsin. If protein denaturation and release of trypsin are both present the natural mechanisms for protection against autolysis no longer suffice and the organ is gravely endangered."

4. Parenchymal Ischaemia

The next theory postulated is that of parenchymal ischaemia. The majority of patients from whom material can be obtained for microscopic study show vascular thrombi and evidence of pancreatic infarction. Ischaemia in combination with obstruction and activation of enzymes may be the final explanation. Vascular insufficiency caused by vascular spasm or thrombosis leading to hypoxia, cell damage and release of intra cellular enzymes is one possible mechanism.

There are substantial findings which partially support this concept.

1. Nemir and later Anderson could consistantly induce acute pancreatitis by incubating human blood for 24 hours with pancreatic secretions and injecting the mixture into the pancreatic parenchyma of animals. The mixture produces irreversible vascular injury, spasm and thrombosis and parenchymal necrosis within 2 hours of introduction. They feel that blood incubated in pancreatic enzymes produces toxins which cause irreversible damage. As yet, these toxins are unknown.

In the human disease trypsin and blood are mixed together at body temperature in the gland.

2. Again McPhedran,[2] in his search for the truth, was stimulated to carry out extensive study using 0.1% noradrenalin as a vasopressor substance the pancreas of 73 dogs was infused by 5 basic means. These were: intraductally; intra arterially; intra venously; interstitially and intermittent intra-arterial. Some dogs had their pancreatic ducts tied off, others were given Urecholine to stimulate the gland. Others still had both. Lethal hemorrhagic necrotic pancreatitis was found in 25% of the animals as a whole. One group, the one which had an intra arterial infusion, duct ligation and Urecholine had a 67% incidence of acute pancreatitis. It was concluded that vascular spasm or thrombosis may play a role in the pathogenesis of the disease but are not the only causes.

5. Allergic Theory[7]

The idea that pancreatic necrosis might be on the basis of allergy, has existed for many years. Thal and Brackney (1954) produced some very interesting work by inducing a local Swartzman reaction in the pancreas of rabbits and goats. They injected a small amount of meningococcol or E. Coli toxin under low pressures, into the pancreatic ducts and then 24 hours later gave a further dose intravenously. In most cases they produced severe acute pancreatitis. It is not too difficult to postulate a similar human mechanism. Coliform bacteria are commonly excreted into the bile from the liver. In a person with cholelithiasis, a stone could be passed and become impacted at the lower end of the common bile duct. The bacteria might release toxins, which because of the obstruction would diffuse or regurgitate into the pancreatic ducts thereby sensitizing the gland. If in the next day more toxin gained entry into the blood stream a Swartzman reaction would occur producing a necrotic gland. Only 3 or 4 cases have been reported however which fulfill all the criteria for an allergic reaction.

6. Auto-Immunity

A theory which seems to be included in attempts to explain any poorly understood diseases is the auto-immune theory. Dreiling[15] in 1960 implied that all mechanisms listed above are quite naive. He suggests other factors must be present, namely a change in method of excretion from exocrine to endocrine. This would raise circulating trypsin levels which by autocatalysis would activate trypsinogen and chymotrypsmogen to activated forms which in turn would damage pancreatic cells releasing cellular proteins. Antibodies forming against these "foreign proteins" would destroy the pancreas. Very little experimental evidence exists to support this theory. Thal however was demonstrated anti pancreas antibodies in some of his experiments. Auto immune mechanisms in regard to pancreatitis for the present remain esoteric and not fully investigated.

7. Duodenal Reflux[6]

The theory of duodenal reflux is to my mind very significant. The ampulla of Vater is lined by delicate mucosal folds or valvules, which possibly function to prevent regurgitation of duodenal contents. If these valvules become deficient due to passage of gall stones or chronic alcoholic duodenitis, or if duodenal pressures become great enough to make these valvules incompetent, duodenal contents regurgitate into the pancreatic ducts and acini. The duodenum contains enterokinase and acid which can activate pancreatic enzymes. It also contains bile, chymotrypsinogen and trypsinogen as well as their active forms, and lipases peptidases nucleotidases and elastoses. Duodenal contents and activated enzymes could digest practically any protein including pancreatic tissue. Once acinar cells are damaged more precursor enzymes and other substances become released which destroy more pancreas and a chain reaction is set up.

A. D. McCutcheon offers the following facts to support the theory of duodenal reflux.

(1) If one creates a blind duodenal loop as Pfeffer did in 1957 by closing each end of the duodenum with sutures and then performing a gastrojejunostomy; and if one ties off the common bile duct but allows the pancreatic duct to drain normally—acute pancreatitis can be induced in laboratory animals. In BaSO4 were placed into the duodenum, it was later found in the pancreatic ducts. Pancreatitis could be prevented in these cases if the pancreatic ducts were tied. This shows that duodenal reflux must have been the cause of the pancreatitis Wallenstin (58) presented some analogous human proof when he reported several cases of pancreatitis following Billroth II partial gastrectomies in which the afferent loop became obstructed. In both examples high duodenal pressures probably forced open the papillary valvules. If these valvules are atrophied perhaps reflux can occur at physiological duodenal pressures.

(2) Further favourable evidence, is that duodenal pancreatic reflux occurs in about 40% of patients with cholelithiasis or choledocholithiasis (Hickin and McAllister) (by cholangiography).

A CONCEPT OF THE PATHOGENESIS

Despite the fact that the disease has been investigated extensively, no one knows what causes pancreatitis. Initially something must occur which disrupts the integrity of the gland and either lysis or ruptures tiny ducts or acini. The injury may vary from protein denaturation of cell membranes to cellular destruction. Secondly, active enzymes attack and destroy susceptable cells. What determines the severity of an attack, is more than likely the degree of the initial insult to the gland. After this the following events occur in the pathogenesis of severe acute pancreatitis.

Damaged cells release histamine, seratonin and kallikrein which is a plasma kinin forming enzyme. Kalli-

krein combines with a plasma and globulin to produce bradykinin, a nonapeptide with potent vasodilating properties. These 3 chemicals and probably others, induce local vasodilatation. This in combination with vascular damage involved by enzymes causes plasma to exude into the parenchyma of the gland. Tiny vessels become eroded and minute hemorrhages occur. Trypsin incubates with this blood and within hours toxins are released which induce thrombi in other vessels. As the gland swells, lymphatics and veins are obstructed causing further oedema and vascular stasis. Areas of the gland which have been infarcted become anoxic and release their complement of enzymes which are activated almost immediately. Blood oozes into the necrotic areas. Neutrophils attempt to limit the destruction by surrounding the infarcted areas. Systemic leucocytosis results. Large quantities of plasma are lost into the parenchyma of the pancreas; the peritoneal and retroperitoneal spaces and the omental bursa causing the hematocrit and hemoglobin levels to rise deceivingly. Blood too has been lost and haemolyzed. Swelling can obstruct the common bile duct causing a post-hepatic jaundice.

Nerve endings in the gland become anoxic and swollen and the patient experiences pain in the distribution of T5 to T9 in the epigastrium, LUQ, RUQ or in the infra scapular area of the back, Irritation of the diaphragm may cause shoulder tip pain.

As acinar cells die, amylase may be released. Serum levels may remain normal at 150 Somogyi U/100 cc or reach values as high as 2000 units within hours. Values are elevated in most cases for 1 to 2 days, but may drop to normal within 12 hours of the onset of the attack. The urinary amylase concentration is 5 to 6 times greater than that of serum and remains elevated for about a day after serum levels become normal. It should be noted here, that carcinoma of the lung, cholecystitis, peptic ulcer, renal colic and bowel obstruction can also raise serum and urinary levels of amylase to the same degree as pancreatitis.

Within hours profound shock and an adynamic ileus ensue. These are due to at least two factors. The first factor is hypovolemia due to the loss of 3 to 4 litres of plasma and whole blood. The second factor concerns kallikrein. This polypeptide is found in high levels in the blood and its presence here causes peripheral vasodilatation and intravascular clotting.

Serum lipase, for some reason, does not become released in large quantities till serum amylase levels start to fall, but they remain elevated for 5-7 days. Lipase splits neutral fats producing glycerol and fatty acids, calcium and fatty acids saponify to produce insoluble calcium soaps. On about the 3rd day of the disease serum calcium levels may fall to tetanic levels in many cases. When lipase and other digestive enzymes erode parietal peritoneum localized epigastric pain and moderate rigidity occur.

The earliest complication is hyperglycemia due to injury and inflammation of the islets of Langerhans. A later and more serious complication is secondary bacterial infection of the necrotic tissue. This is not an uncommon finding.

The foregoing pathogenesis describes a severe acute necrotic hemorrhagic pancreatitis. The majority of attacks are less severe and many are so mild that they probably are never diagnosed.

DIAGNOSIS

Diagnosis is usually on clinical and laboratory grounds.

CLINICAL PICTURE

This characteristically presents with sudden severe upper abdominal pain. The degree varies with the pancreatic insult. Milder forms give epigastric pain, frequently radiating through to the back below the scapulae or along the right or left rib margins. Shoulder tip pain may be present. More extensive forms cause much more severe pain associated with prostration, tachycardia fever and shock. These patients usually develop an adynamic ileus and vomit profusely (sometimes fecal in nature).

Other clinical signs may be:

(1) Marked abdominal tenderness.
(2) Rebound tenderness.
(3) Moderate rigidity.
(4) Absent bowel sounds.
(5) Mild jaundice (in 3 to 4 days in about 25%).
(6) Blue-grey discolouration of skin in epigastrium.

LABORATORY PICTURE

(1) Hemoglobin and hematocrit both elevated.
(2) White count elevated 8 to 20,000 P.M.N.'s.
(3) E.S.R. elevated—May surpass 100 min.
(4) Electrolytes—Na, K, Cl may all be low.
(5) Metabolic Alkalosis (hypochloremic).
(6) Plasma proteins may be low.
(7) Serum Amylase—may or may not be elevated; or may be transcently elevated and normal within 12 hours. Usually elevated 200-2500 for several days with higher (2 to 6 times) levels in urine which persist a day or so often serum levels are normal.
(8) Serum Lipase increases as amylase drops. Stays elevated for 5 to 7 days.
(9) Serum Calcium may drop in 2 to 11 days down to tetanic levels i.e. 7 mg/100cc.
(10) Glycosuria occurs during the acute phase in 5 to 10% of cases.
(11) Van den Bergh positive in 25%.
(12) Urine output may decrease. pH basic.

RADIOLOGICAL FINDINGS

(1) Moderately distended gas filled loops of intestine. The ileus often affects jejunal loops near the pancreas producing the "sentinal sign".

(2) The "cut off sign"—a barium enema gives the appearance of a large bowel obstruction in the transverse colon.

DIFFERENTIAL DIAGNOSIS

(1) Biliary colic and acute cholecystitis.
(2) Penetrating peptic ulcers.
(3) Perforated peptic ulcer.
(4) Renal Colic
(5) Acute Phlegmonous Gastritis.
(6) Mesenteric Thrombosis.
(7) Volvulous.
(8) Dissecting Aneurysm.
(9) Myocardial Infarct.
(10) Hiatus Hernia with esophagitis.

TREATMENT

The emergency treatment of acute pancreatitis is conservative. A few guiding principles should be followed.

A. Treat shock and electrolyte abnormalities.

B. Suppress pancreatic exocrine function.

C. Prophylatic antibiotic therapy.

D. Trasylol?

As soon as a diagnosis of acute pancreatitis is suspected following history, physical and laboratory examination, the patient is catheterized and continuous naso-gastric suction is initiated. Input, output, vital signs, hemoglobin and electrolytes are watched closely for several days.

A. Shock

One should regard pancreatitis as a severe internal burn. An average three to four litres of plasma and whole blood are lost; the losses of plasma being greater than those of whole blood. This gives a deceitfully high hemoglobin level. During the first 24 hours three to four litres of blood and plasma should be replaced. In addition the volume of the urinary output and gastrointestinal secretions should be replaced as normal saline. The rate of administration is determined by clinical improvement of the shock, urinary output and hemoglobin—hematocrit levels. A central venous catheter may be inserted in the jugular vein to measure venous pressure and prevent overloading.

Potassium as Kel should be given in amounts about equal to 80 meq per 24 hours.

Other electrolytes and Calcium may be added as laboratory findings indicate.

If shock persists despite vigorous replacement therapy, hydrocortisone may be added as an alpha-adrenergic blocking agent. Isuprel may be used to stimulate beta-adrenergic nerve endings. These measures cause vasodilatation of skin and renal vessels and prevent renal shut down.

After the first 24 hours fluid replacement is about equal to 600cc plus losses from naso-gastric and urinary losses. Kel is continually replaced.

The relief of pain is important, for some authors feel it contributes to the shock. One hundred mg of Demerol will at least make the patient feel better and lessen anxiety. At times pain is so severe that a splanchnic nerve block or epidural anesthetic is required to give relief.

B. Suppression of Pancreatic Stimuli

Supression of pancreatic exocrine function is achieved in several ways. First, the continuous naso-gastric suction removes pancreatic stimuli, i.e. stomach acid, peptones and fats which normally stimulate the pancreas by releasing secretion and pancreozymin from the duodenum. It is also good treatment for the ileus which is present.

Intravenous atropine or other anticholinergics are given in high doses 4-5 times a day, to suppress the stomach and pancreas.

Diamox (or acetazolimide) a carbonic anhydrase inhibitor given intravenously in 250 mg doses b.i.d., achieves the same effect.

Some authors advocate the use of insulin to combat the hyperglycemia that results. The hyperglycemia however is seldom high, in usually transient and not harmful to the patient. The patient, moreover, is insulin sensitive.

C. Antibiotics

Prophylactic penicillin or tetracycline is started immediately because of the high incidence of secondary infections and their product, cysts or abscesses. This is given into the intravenous bottles.

Using this regimen there should be about a 15% mortality rate in severe cases. (Classen and Hooper, 119 cases, 17% rate, June 64 Am. Surgeon).

D. Tryasylol

Around 1956, a new drug called Trasylol was introduced in Germany which was reputedly specific in acute pancreatitis. Trasylol is a trypsin-kallikrein inhibitor extracted from bovine parotid glands. When this drug is administered to animals, at the time pancreatitis is induced, there is a significant drop in the severity and mortality of the condition.

It is interesting that serum enzyme levels and autopsy findings are not usually altered when trasylol is used. McCutcheon finds the pancreas to be involved to a much lesser degree in his experiments using the drug, though the remaining findings are similar to above.

There are conflicting reports regarding the usefulness of Trasylol in the treatment of human pancreatitis. Before introduction of the drug, Mauer in Munich stated that the overall mortality of the disease in Europe was 60 to 80%. In one of his series employing conservative treatment plus Trasylol he reports a 35% mortality. Forell, using similar treatment, had a 10% mortality.

Nardi in Boston states that improvement in either morbidity or mortality is not convincing in his hands.

It seems to me that for this drug to be effective, it must be given at the start of the process. Since most cases don't present till there at least some degree of pancreatic destruction, it doesn't seem reasonable to believe that this drug is of great significance.

SUMMARY & CONCLUSION

The majority of cases will respond favourably to conservative treatment, without Trasylol within a week. Intravenous should be continued till bowel function returns. At this time the D-tube and urinary catheter may be removed and oral fluids started. Oral drugs may be started and the diet gradually increased. Massive hemorrhage peptic ulcer, abscess or cyst formation may require immediate surgical intervention.

About four to six weeks after a non-complicated attack a cholecystogram and gastro-intestinal series should be ordered to rule out gall bladder disease or penetrating ulcers. If the gall bladder is diseased it should be removed electively.

EDITOR NOTE

This paper was presented last year at an AOA Society meeting by the author when he was in his last year at University of Toronto Medical School. Because of its outstanding quality, we persuaded the author to let us kindly publish this review.

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Abstract

Macroglobulins in Rheumatoid Arthritis and Other Diseases

Nanna Svartz, M.D.: The Jour. of the Am. Med. Assoc., Vol. 194, No. 5, November 1, 1965 pp. 516 - 522.

A method of purifying the rheumatoid factor (RF) and various investigations performed on the isolated factors are discussed. It is stated that the amino acids of the RF exhibit no definite differences from the amino acids of macroglobulins in the blood of healthy persons, and concluded that the manifest biological dissimilarities between the two must be due to their different molecular structure.

Various methods of dissociating the RF were tried. The hemagglutinating capacity of the different fractions was tested.

Autoradiographic studies were made with RF labelled with iodine 125. The labelled substance was injected intravenously into mice. The RF showed almost exclusive affinity for the connective tissue in skin, joint capsules, tendons, and walls of vessels. Radioactivity was also observed in the epiphyses of bones and in the intervertebral cartilage.

The RF was found to have excellent antigenic capacity. Whether it is, itself, an antibody remains in doubt. The author considers it to be an abnormal metabolite of certain cells (lymphocytes or fibroblasts) perhaps in response to agents such as viruses, bacteria or toxins.

In comparing the macroglobulins of different diseases, e.g. rheumatoid arthritis and lupus erythematosis this author finds chemical differences. The best methods for demonstrating these differences, at present, are ultracentrifugation the hemagglutination test, and cold precipitation. M.S.

Chronic Pancreatitis

B. K. Mohindra 6T6

Chronic pancreatitis is an ill-understood entity. There is no clear-cut aetiology, clinical picture or precise classification.

Interest in chronic pancreatitis was revived by Comfort at the Mayo Clinic. He used the term "chronic relapsing pancreatitis" to describe a group of cases characterized pathologically by progressive destruction of the gland and clinically by repeated sublethal attacks of acute pancreatitis. The pancreatic tissue is damaged with each attack and the end result is extensive fibrosis with destruction of acinar tissue, islet tissue, ductal obstruction, pseudocyst formation and calcification in many instances. The destruction of acinar and islet tissue is reflected in varying degrees of pancreatic insufficiency and diabetes. The clinical manifestations may be transient or may not be recognized during the early stages but become manifest as the disease reaches an advanced stage.

In acute pancreatitis, if the destructive process is not too severe, there is a complete restoration of both pancreatic structure and function. When pseudocyst or abscess formation complicate acute pancreatic necrosis, it is remarkable how completely restitution may take place. Irreversible damage, leading to chronic pancreatitis, seems to be a relatively uncommon sequel of acute pancreatic necrosis. If there is ductal obstruction which may have caused the initial attack or resulted from an acute attack, recurrent acute attacks may occur and lead to chronic pancreatitis.

DEFINITION

Chronic pancreatitis denotes the sclerotic, inflammatory processes of differing aetiology which affect the pancreas.

CLINICAL CLASSIFICATION OF PANCREATITIS

The following classification was adopted at a symposium on the aetiology and pathological anatomy of chronic pancreatitis held in Marseilles in 1963.

(1) *Acute pancreatitis*

(2) *Relapsing acute pancreatitis* (In these two acute forms clinical and biological restitution of the pancreas takes place if the primary cause or factors are eliminated.)

(3) *Chronic relapsing pancreatitis* (Defined as chronic pancreatitis with acute exacerbations.)

(4) *Chronic pancreatitis* (In these two chronic forms, residual pancreatic damage—either anatomical or functional persists even if the primary cause or factors are eliminated.) Chronic pancreatitis may result from chronic relapsing pancreatitis or it may manifest itself from the first as a chronic disease. The distinctions between Groups 3 and 4 is clinical and not morphologic.

AETIOLOGY

The aetiology of chronic pancreatitis has not been well-established. Various factors and mechanisms are involved. Indeed, in many cases no aetiological factor may be established.

1. Alcoholism

The exact role of alcoholism in the production of chronic pancreatitis is not known. The incidence of alcoholic pancreatitis is higher in the United States, France, Australia, South Africa and is negligible in Britain and other countries in Europe as Switzerland and Czechoslovakia.

Pancreatic calcification has been shown to be more common in patients with history of alcoholism.

2. Pancreatic Ductal Obstruction

Many European and American observers have shown that any obstruction to the main pancreatic duct may result in chronic pancreatitis. In the 44 cases studied by Howat in England,[5] in roughly half the cases an obstructive factor could be implicated and in half no aetiological factors could be identified.

Among the lesions that may obstruct the main pancreatic duct and lead to chronic pancreatitis are included Vaterian stenosis (additis), traumatic stricture, stone-formation, papilloma of ampulla of Vater, cancer and duodenal obstruction.

3. Malnutrition

Subnutritional states, in addition to affecting the liver, may also produce changes in the pancreas. Chronic dietary protein deficiency (Kwashiokor) is linked to a form of chronic pancreatitis. It has been suggested that a very high carbohydrate or fat diet, in combination with a negligible protein intake may result in severe depletion of normally protein-rich acinar cells with the resultant atrophy of the pancreas.

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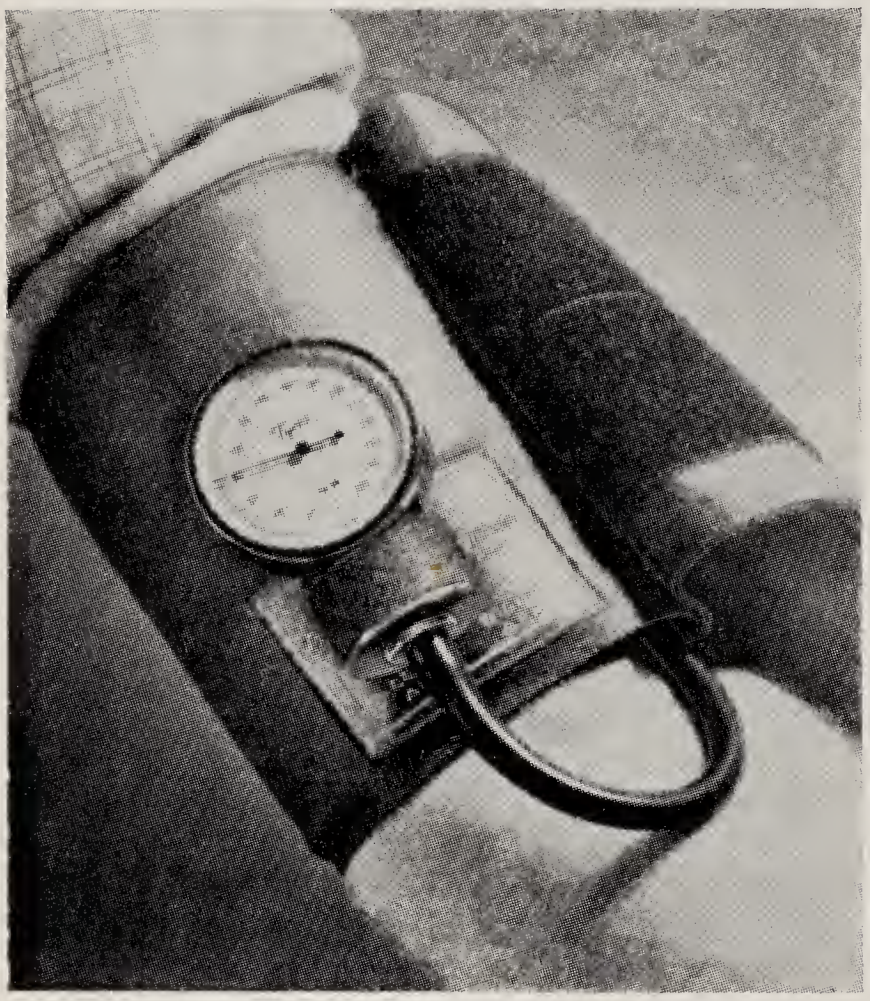

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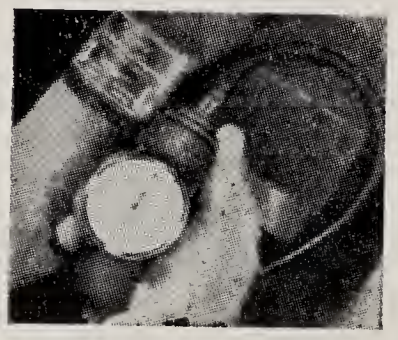

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Chronic pancreatitis is also found in patients with hemachromatosis—haemasiderosis.

4. Gall Bladder Disease

The presence of gall bladder disease is a common finding in chronic pancreatitis. Fisher, Fisher and Selkar showed that no damage results as a result of bile reflux into the pancreatic duct at normal pressure and in absence of infection. But if there is spasm or stenosis of the sphinctre of Oddi, the resultant rise in pressure together with the presence of bile in the pancreatic duct, will produce degenerative changes in the pancreas. These changes are accentuated if infection is present as well.

5. Post-operative Causes

A few cases have been reported to result following surgery. Morrin and Duncan described 3 cases of post-operative pancreatitis which occured in patients who had deep penetrating peptic ulcers.

6. Miscellaneous

Heredity, hyperlipaemia, hyperparathyroidism, virus and auto immunity have been implicated as causes of chronic pancreatitis.

Generally pancreatic ductal obstruction and alcohol are the two most common factors found in association with chronic pancreatitis.

PATHOLOGY

Pathologically there is destruction of acinar tissue with an irregular sclerosis and fibrous tissue proliferation. This may be focal, segmental or diffuse.

The islet cell tissue is well preserved till the late stages of the disease.

Abscess, pseudocysts and cysts may also occur.

There is dilation of the various parts of the duct system. Associated with this is the presence of strictures and stones. The incidence of calicification is variable and is mainly present as stones within the ducts. Parenchymatous calcification is uncommon.

CLINICAL FEATURES

Frequency

Chronic pancreatitis is an uncommon disease. Primary acute pancreatitis has a far higher incidence than chronic pancreatitis. In Dublin, Ireland, Fitzgerald encountered 53 cases over a period of 8 years. The incidence of chronic pancreatitis is higher in the United States than in the United Kingdom. Whether this is related to a higher incidence of alcoholism has not been established.

The usual onset is in the 5th - 7th decades of life although much earlier onset has been reported in several cases.

Whereas Gambill and Comfort showed a male preponderance of this disease in North America, Fitzgerald showed that in his series in Dublin, women were more frequent sufferers.

SYMPTOMS

(a) Acute Phase

In the early stages of the disease *pain* is the main presenting symptom. If the whole of the pancreas is involved, the pain is diffuse but is felt more in the upper central abdomen. It usually radiates to the centre of the back and one or both loins. If the head of the pancreas is involved during the acute phase, the pain tends to be in the right hypochondrium and referred to an area below the inferior angle of the right scapula. If the body is involved the pain tends to be in the mid epigastrium, radiating to the spine in the midline. If the tail is involved pain tends to be in the left hypochondrium, radiating to the inferior angle of the left scapula.

Typically the pain tends to be diffuse and the patient covers the affected area with the palms of his hands. With subsequent attacks, pain may be experienced at a site different from previous attacks. The patient may have difficulty in describing the pain—it is deep-seated and may be described as burning, a heaviness, a cramp, a lump or a gnawing. Characteristically the pain is persistent, wears down the patient, not as severe as that of acute pancreatic necrosis and usually lasts for several days—a feature which distinguishes it from biliary colic or from a simple ulcer. It is not relieved by vomiting or by alkalis. This pain is made worse when the patient lies supine and betters when the patient sits in an erect position. The pain may simulate that of coronary heart disease.

The precipitating factors of an acute attack include (a) a heavy meal accompanied by alcohol in the preceding twelve to twenty-four hours (b) by taking opiates such as compound codeine tablets after alcoholic excess (c) or simply following an intake of large amount of alcohol. *Other symptoms* which may or may not be present are nausea and vomiting, jaundice, fever, looseness or stools and abdominal distension. There may be some tenderness and guarding.

The lab findings do not differ from acute primary pancreatitis and include leukocytosis, hyperenzymemia and increased concentrations of amylase and lipase in the urine.

(b) The Remission Period

This is an asymptomatic stage. There may be a mild dyspepsia, loss of appetite, weakness and weight loss.

Sometimes an average of five years may lapse after the initial attack before the diagnosis of chronic pancreatitis is established. If diagnosis is made earlier it is possible to arrest the progression of the disease.

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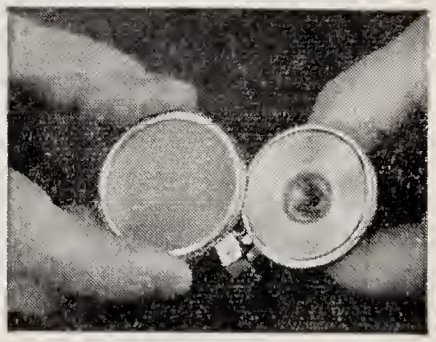

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(c) Late Stage

With the destruction of the gland, an advanced stage of chronic pancreatitis is reached. This is characterized by diabetes, steatorrhoea and calcium deposition within the gland.

Chronic pancreatitis may present as non-relapsing, painless, pancreatitis, without any history of previous attacks. The clinical picture is one of pancreatic insufficiency.

INVESTIGATIONS

(1) *Routine Lab Tests*

These should include an estimation of serum bilirubin, blood calcium, alkaline phosphatase, blood sugar and sedimentation rate.

(2) *Stool Examination*

This is a simple test for pancreatic insufficiency. Both gross and microscopic examinations should be carried out.

(3) *Blood and Urine Pancreatic Enzyme Tests*

Serum amylase and lipase levels are significantly elevated during painful episodes, but are usually normal during remission. Generally, serum and urine amylase and lipase are a less valuable index of chronic than acute pancreatic disease.

(4) *Serum Pancreozymin—Secretin Test*

The pancrease can be stimulated with secretin, followed by pancreozymin. Serum amylase and lipase are estimated before and after stimulation. A significant rise of serum enzymes normally occurs after stimulation. This is true of the earlier stages of chronic pancreatitis when acinar tissue and function are present. With severe acinar destruction and in normal patients no appreciable rise is noted. This test is also positive in the cancer of the pancreas.

(5) *Glucose Tolerance Test*

A diabetic type curve may be obtained in the later stages of the disease.

(6) *The Duodenal Secretin Test*

This is a very accurate method of determining the status of the exocrine secretion of the pancreas.

The characteristic secretary defect in patients with chronic pancreatitis is an inability to secrete a juice of normal high bicarbonate content. There is a marked decrease in the volume of flow and enzyme secretion in the presence of pancreatic calcinosis. This test can also be used to differentiate chronic pancreatitis from pancreatic carcinoma.

(7) *Radiography*

A. Plain X-ray abdomen —
These may reveal calcification within the pancreas.

B. Barium Studies —
May show distortion, widening or obstruction of the pyloric and duodenal loop, due to an enlarged pancreas.

C. Pancreatograms —
To show pancreatic duct obstruction.

TREATMENT

A. Medical Management

The management of chronic pancreatitis includes the following:

(1) *Dietary Therapy*. Diet is an important part of treatment. A bland diet with restriction of fat (especially cooked fats), adequate protein, vitamins and a relative increase in carbohydrate should be prescribed. These meals should be small and be taken at frequent intervals. The foods should also be low in roughage and secretory stimulants. Alcohol, in any form, should be avoided for an indefinite period. Opiates, including compound codeine tablets should not be used.

(2) *Substitution Therapy*: When there is a deficiency of external pancreatic secretion, pancreatic substitutes such as Viokase, Pancreatin or Cotazym should be used.

Patients with pancreatic diabetes mellites respond to oral hypoglycaemic agents.

(3) *The relief of pain*: This is a difficult problem to manage. There is no ideal analgesic for pancreatic pain. Pethidine and morphine can be used only sparingly because of the danger of addiction. When opiates are used parenterally, glyceryl trinitrate tablets may be used sublingually or aminophylline intravenously to mitigate the resulting spasm of the sphinctrer of Oddi.

B. Surgical Management

Indications for surgery include:

(i) Biliary tract disease which is amenable to surgery.

(ii) Mechanical obstruction to the outflow of pancreatic juice to account for recurring attacks.

(iii) The presence of complicating lesions such as perpancreatic abscess or pseudocyst.

(iv) Relief of pain not alleviated by conservatine measures.

(v) The possibility of carcinoma of the pancreas.

CONCLUSION

A brief review of chronic pancreatitis is presented. The outlook for the patient with advanced stages of chronic pancreatitis is not very good. All the efforts should be concentrated to diagnose the condition earlier and correct the precipitating factors as alcoholism and biliary tract disease.

Carcinoma Of The Pancreas

K. W. Johnston 6T6

The pancreas is the source of tumours of many histological types (Table I) but by far the commonest is the malignant tumour arising from pancreatic ducts or acini—namely CARCINOMA. I think it can be reasonably said about this tumour that when it is treatable it is rarely diagnosable and when it is diagnosable it is rarely treatable.

TABLE I:
A CLASSIFICATION OF PANCREATIC TUMOURS

Origin	Tumours
ducts or acini	adenoma cystadenoma papilloma CARCINOMA (95% pancreatic tumours)
islets	benign or malignant beta cell tumour (Clinically presents with symptoms of hypoglycemia) benign or malignant delta cell tumour (Clinically presents as Zollinger-Ellison Syndrome-excessive gastric secretion, recurrent peptic ulceration)
interstitial tissue	numerous possibilities
extrapancreatic (secondary)	numerous possibilities

INCIDENCE

Carcinoma of the pancreas represents about 1-2% of all cancers (Berk) and the incidence appears to be rising (Dorn and Cutler). Approximately 0.05% of admissions to general hospitals are due to this disorder (Sloan and Wharton). Males are afflicted about twice as often as females and most cases occur between the ages of 55 and 70. Rare cases have been recorded in infants and children, but according to Bell's study 97% occurred over the age of 40.

ETIOLOGY

Virtually nothing is known about the etiology of cancer of the pancreas; however, three observations are worth noting. First, benign cystadenomata are known to undergo malignant change. Second, hyperplasia and metaplasia are noted at autopsy frequently in patients with cancer of the pancreas (Sommers, Murphy, and Warren) but there is no evidence of link this with the etiology of cancer. Third, recent papers have noted the higher incidence of pancreatic cancer in patients with chronic pancreatitis and pancreatic lithiasis. In a series by Paulino-Netto and others, cancer of the pancreas occurred in 6% of patients with chronic pancreatitis and in 25% of cases with pancreatic calcification. In those cases associated with calcification, chronic irritation is the suggested etiological factor.

GROSS PATHOLOGY

The pathology of cancer of the pancreas is important in understanding the clinical presentation and the problems encountered in its surgical treatment.

Glenn summarized over 1200 reported cases and noted that the head of the pancreas was involved in 60%, the body and tail in 30% and the whole gland in 10%.

The pathology of cancers of the head and those of the body and tail of the pancreas is essentially the same except for the organs involved by invasion and the stage at which the lesion is seen clinically and surgically. Because of these similarities, cancer of the head of the pancreas will be considered in more detail.

In cancer of the head of the pancreas the lesion is an irregular, nodular, firm mass which obliterates the normal pancreatic tissue. On section, a gray-white, scirrhous, homogeneous tumour mass is seen replacing the normal yellow lobulated architecture of the pancreas. Bowden suggested that because of the surrounding zone of pancreatitis, the tumour may account for less than one third of the mass.

The associated changes are the result of involvement of (1) Wirsung's duct, (2) common bile duct, (3) local veins, (4) nerves and (5) bowel. The pathology resulting from involvement of each of these structures will be considered.

(1) Wirsung's Duct is obstructed by direct invasion or by compression by the tumour or adjacent lymph nodes. As a consequence, it is usually dilated and can be palpated at the junction of the upper and middle thirds of the gland. In rare cases cystic spaces may develop. As the result of the inflammatory reaction associated with the obstruction, fibrosis occurs and the distal pancreas becomes firm, and enlarged; hence, the limits of the tumour become ill-defined and the extent of the tumour difficult to determine.

(2) The Common Bile Duct is compressed and invaded, the hydrostatic pressure increases, and the extrahepatic bile ducts dilate. As a result of increased hydrostatic pressure in the extrahepatic bile ducts, the gallbladder dilates. Courvoisier noticed this and suggested that dilation of the gallbladder in the presence of obstructive jaundice usually meant malignancy at the lower end of the common duct rather that a stone. This "law" is based on the premise that a stone implies the existence of chronic cholecystitis and that a chronically inflamed and fibrosed gallbladder cannot become dis-

tended. An alternate explanation suggests that with the intermittent obstruction associated with a stone, the hydrostatic pressure is lower and the gallbladder is not as easily distended. Also as a result of obstruction of the extrahepatic bile ducts, the liver enlarges and enlarged intrahepatic ducts may be seen on cross-section. If obstruction persists ascending cholangitis may supervene. Much later in the disease the liver parenchyma may be destroyed by secondary biliary cirrhosis or metastases.

(3) Local Veins may also be compressed or invaded—namely, the interior vena cava, the superior mesenteric vein and the portal vein. Involvement of the portal vein is common and may account for ascites and early widespread metastases to the liver.

(4) The Celiac Plexus and the posterior abdominal wall may be invaded and this undoubtedly accounts for much of the severe pain that is often seen.

(5) Tumour eventually encroaches on the stomach, duodenum and transverse colon producing defects which can be seen radiologically.

Four other conditions are occasionally associated with carcinoma of the pancreas, namely, (1) hemorrhagic phenomena (2) duodenal obstruction (3) functioning metastases and (4) thrombophlebitis. As a consequence of complete extrahepatic biliary obstruction *hemorrhagic phenomena* are frequent. In the presence of obstruction, bile salts do not reach the gastrointestinal tract, less vitamin K is absorbed, less prothrombin is formed and a coagulation defect results. *Duodenal obstruction* may occur late in the disease but White reported 4 cases presenting as acute duodenal obstruction without jaundice. *Functioning metastases* in carcinoma of the pancreas are very rare but Osborne reported a case with subcutaneous fat necrosis occurring as the result of digestive ferments liberated from metastases. *Thrombophlebitis* according to some authors is a frequent association with carcinoma of the pancreas; however, others feel that this co-relation is not valid. Lieberman noted that thrombophlebitis frequently occurred in association with other neoplasms *not* just with cancer of the pancreas. The thrombophlebitis is characteristically migratory, resistant to anticoagulants and shows an increased risk of pulmonary embolism.

Cancer of the body and tail of the pancreas differs from cancer of the head in that it occurs in a more silent area of the gland and can grow for longer periods of time without producing obvious clinical manifestations. The gross pathology of carcinoma of the body and tail differs from carcinoma of the head of the pancreas in the following respects: this site is only half as common; the tumours are often large and palpable; there is greater tendency to thrombophlebitis; and the spread is superiorly and inferiorly in the retroperitoneal space occasionally involving the adjacent left adrenal, kidney or the spleen. Involvement of the splenic vein is not uncommon and massive liver metastases or splenic infraction may result.

MICROSCOPIC PATHOLOGY

The typical microscopic picture is that of adenocarcinoma (ie: a glandular pattern) with abundant fibrous tissue separating the glandular structures. Some distinguish the tumour on the basis of the cell of origin—from acini if the cells are darkly stained and granular, or from ducts if they are more clear and contain mucus secretions. This distinction is often difficult to make. A second histological variation is the rare anaplastic tumour. Two other microscopic findings have been observed. Drapiewski noted that there was invasion and extension along perineural lymphatics, a fact that may help explain the poor prognosis. Cattell and Warren observed that there was often a malignant deposit at the duodenal opening of both the main and accessory pancreatic ducts but without submucosal spread or other evidence of direct or lymphatic spread. This raised the suggestion that these implants may occur via the lumen and yet cancer cells are found infrequently in duodenal drainage.

SPREAD

Spread of carcinoma of the pancreas is by (1) direct invasion as already described, (2) the lymphatics to the local pancreaticosplenic, subpyloric and pre-aortic nodes and to more distant areas, (3) blood or (4) peritoneal seeding.

SYMPTOMS

The symptoms associated with carcinoma of the pancreas are variable and depend to some degree on the part of the gland involved. The onset is usually insidious with vague gastrointestinal symptoms and weight loss for 2-3 months when the head of the gland is involved, and for 7-8 months when the body and tail are involved. When the head is involved, three symptoms are commonly found: (1) extreme weight loss (2) pain (3) jaundice. In carcinoma of the body and tail of the pancreas pain and weight loss are common but jaundice is a late complaint and more often due to compression of the common duct by metasatic nodes than by direct invasion (Robbins). These three common symptoms will be discussed individually.

Weight loss is usually severe (20-25 pounds) and is the most consistent symptom. This may be due to the tumour, malabsorption, vomiting or anorexia.

The *pain* of carcinoma of the pancreas is located anteriorly between the xiphoid and umbilicus in the midline or slightly laterally or in the back or in both boring from back to front or front to back (Harrison). The severity varies from the more common or vague poorly localized abdominal discomfort to unrelentless gnawing. *At first* the pain tends to midepigastric, paroxysmal, and

aggravated by the intake of food. If Wirsung's duct is blocked by tumour, when food is taken, reflex stimulation of secretion from the acini may increase the intraductal pressure cause episodic pancreatitis and produces a picture which resembles relapsing pancreatitis. *Later,* with extension of the tumour, the pain is more severe, persistent, and boring through to the back. The pain associated with carcinoma of the body or tail may be severe and characteristically is aggravated by lying flat and relieved by sitting forward or lying on the right side with legs drawn up (Inglefinger's sign). Presumably in these cases the celiac plexus has been invaded by tumour or the peritoneum is stretched over the growth or past abdominal wall and these positions take some of the stretch off the nerves.

Jaundice occurs in 70% of carcinomas of the head of the pancreas and 40% of those involving the body and tail (Berk) and contrary to previous opinions is usually associated with pain. The jaundice is progressive and steady reaching a maximum intensity in several weeks and passing from yellow to olive green terminally. Associated with severe obstructive jaundice are pale bulky stools, dark urine, pruritis, bradycardia, foul breath, dirty tongue and a bleeding tendency.

Many other symptoms may occur. Anorexia, nausea, vomiting, diarrhea or constipation occur in about half the patients. Persistent nausea and vomiting may signify duodenal obstruction. Fever and chills may occur from infection of the biliary tree or pancreatic duct system. In addition, symptoms due to thrombophlebitis, diabetes or metastases may be present.

In summary, severe weight loss occurs in 90%, pain in 80% and jaundice in 70% if the head is involved or 40% if the body and tail are affected.

PHYSICAL EXAMINATION

Physical examination is usually not very fruitful. Any signs that are elicited either indicate late disease or reflect changes, occurring secondary to involvement of the biliary tract.

In *cancer of the head* of the pancreas, physical examination usually reveals weight loss, jaundice, a palpable gallbladder in 50-65% of the cases (Ackerman), an enlarged liver in 75% of patients and possibly migratory thrombophlebitis. The tumour is rarely palpable. In advanced cases, there will be evidence of metastases.

In *cancer of the body or tail* of the pancreas, thrombophlebitis, and a palpable mass are found more frequently and biliary tract signs are rare and occur late.

LABORATORY INVESTIGATION

Laboratory investigation in the typical case is not helpful. Liver function tests show evidence of biliary obstruction and may show changes secondary to hepatocellular damage from prolonged obstruction.

The hemoglobin is normal in 70% of patients.

Tests of pancreatic function may be abnormal. Examination of the stools shows undigested meat fibers and increased neutral fat and fatty acid content in some cases; however, in the absence of obstruction of Wirsung's duct because of the large functional reserve of the gland there is usually no change in digestion. Serum enzymes are usually normal but amylase may be slightly increased (Cattell). Duodenal analysis of enzyme and bicarbonate after secretin stimulation reveals decreased values.

Cytological studies have proved of limited value, in most series; however, one group in Chicago reported positive cytology in 60% of their cases (Raskin et al). Fasting blood sugar is elevated in about 50% of the patients (Birbaum, Berk).

RADIOLOGICAL CHANGES

The radiological methods of examination of the pancreas include (1) upper GI series (2) intravenous cholangiography (3) percutaneous cholangiography (4) retroperitoneal air insufflation (5) splenoportography and (6) IVP.

Radiological changes were observed on the *upper GI series* in 37% of the patients (Berk) and the abnormalities were distributed as follows: stomach 15%, duodenum 70%, and both in 15% (Beeler). Two signs are usually described—widening of the duodenal loop and the inverted "3" sign. Widening of the duodenal loop is quite characteristic of carcinoma of the pancreas but unfortunately is not common. The inverted "3" sign (Frostberg) is due to enlargement of the pancreas around a fixed ampulla of Vater, is also rarely found, and may also occur in pancreatitis. The more common signs include (1) narrowing, distortion or ulceration of the duodenum or stomach and (2) flattening of the duodenal mucosal folds on the medial aspect of the descending duodenum.

Intravenous cholangiography is useful only if the obstruction is incomplete.

Percutaneous cholangiography may be of value if there is a problem of distinguishing intrahepatic from extrahepatic biliary obstruction. There is the risk of bile peritonitis and the procedure should be done only if operation is planned within hours. The biliary tree will be outlined and a filling defect may be demonstrated.

Retroperitoneal air insufflation is used for tumours of the body and tail in the occasional case.

Splenoportography is not widely used but may show invasion or compression of the splenic or portal veins.

Intravenous pyelograms may help to distinguish cancer of the body or tail of the pancreas from renal masses.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cancer of the head of the pancreas usually involves ruling out other causes of obstructive jaundice—stone, chronic pancreatitis, other periampullary cancers, cholestatic hepatitis and pseudocysts. Cancer of the body and tail may cause pain or exhibit a mass requiring differentiation from numerous lesions and this will not be discussed.

Obstruction of the common duct by a *stone* tends to occur in a younger age group and more commonly in women. There is often a previous history of biliary colic. Obstruction to bile flow is usually intermittent and not complete, there is less weight loss and the gallbladder and liver typically are not enlarged. *Chronic pancreatis or relapsing pancreatitis* generally presents with epigastric pain like that of acute pancreatitis. Later the pain is more persistent, there is nausea and vomtiing, the patient becomes undernourished and if fibrosis is serious enough, jaundice may result. This picture may not be distinguishable from carcinoma of the pancreas. In addition, the gross findings at laparotomy and the histological picture may be difficult to distinguish from that of schirrhous carcinoma. *Cancer of the Ampulla of Vater and periampullary region* usually cannot be differentiated from carcinoma of the head of the pancreas before laparotomy. Distinction is of prognostic importance since in carcinoma of the ampulla operative mortality is less and the 5 year survival much higher. The jaundice of cancer of the ampulla presents earlier, and tends to be somewhat fluctuant as tumour is shed into the lumen of the duodenum; there is less weight loss; and occult blood is detected in the stools in half the cases (Harrison).

TREATMENT

Treatment of cancer of the head of the pancreas is either curative or palliative. Surgical resection of the Whipple type is the usual curative procedure. This involves resection of (1) the distal part of the stomach, (2) the duodenum and proximal part of the jejenum, (3) part of the pancreas and (4) the distal part of the common bile duct. Reconstruction is by (1) gastrojejeunal anastomis (2) anastomsis of the common duct to the GI tract, and (3) anastomosis of Wirsung's duct to the GI tract. In 1951 the operative mortality was 31%. At present is about 10% (Warren).

Palliation is usually surgical by a cholecystojejeunostomy. Radiotherapy, implant radiation, and chemotherapy have also been tried. Treatment of carcinoma of the body or tail is unsatisfactory.

PROGNOSIS

Untreated the prognosis of carcinoma of the head of the pancreas from the onset of symptoms is 6 months on the average (Child, Bell and others). The average prognosis of carcinoma of the body and tail is 10-12 months (Silver and Lubiner).

Surgical treatment of carcinoma of the head of the pancreas gives an average survival of 13 months and 5 year cure rates are from 2-9% (Child, Cattell).

CONCLUSION

From the foregoing, I think some of the problems of diagnosis and treatment of carcinoma of the pancreas can be appreciated. Until such time as we are able to *diagnose* it when it is treatable or *treat* it when it is diagnosable, it will remain one of the most rapidly lethal tumours of the body.

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Pancreatic Pseudocyst

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There are many classifications of pancreatic cysts, but the following is one of the simplest:

1) congenital including
   simple cyst
   dermoid cyst
   fibrocystic disease
   cysts associated with polycystic disease of other organs.

2) retention cysts:
   these are comparable to hydronephrosis since a sudden complete obstruction of a duct produces atrophy of the distal pancreatic tissue but a continuous incomplete obstruction produces dilation of the duct distal to the obstruction and the formation of a thin walled sac lined with epithelium and filled with the external secretions of the pancreas. These have been reported after trauma, chronic pancreatitis and pancreaticolithiasis.

3) neoplastic cysts
   including cystadenoma and cystadenoca. These tend to be multilocular with a honeycomb or spongelike appearance. They consist of cysts with a tense semitranslucent capsule filled with mucus fluid and papillary projections of neoplastic growth.

4) parasitic

5) miscellaneous such as cystic hemangioendothelioma, cavernous hemangiomas and epidermoid cysts

6) pseucocyst with which this paper will deal.

Definition

A pseudocyst is a collection of fluid adjacent to but occasionally in the pancreas surrounded by a sac consisting not of epithelium but of fibrous tissue alone. This absence of an epithelial lining is the basis of differentiating a true from a false cyst. If a retention cyst becomes very large, its lining may undergo necrosis and be histologically indistinguishable from that of a false cyst.

Incidence

Pancreatic cysts are relatively rare and constitute a negligeable percentage of hospital admission. Pseudocysts make up 80-90% of diagnosed pancreatic cysts. They occur primarily in the fourth and fifth decade but have been reported in the very young and the very old. There is said to be a slight male preponderance.

Etiology and Pathogenesis

The pathogenesis of pseudocysts is largely a matter of theory since it has proven difficult to produce pseudocysts in the experimental animal. Lazarus in 1904 produced a cyst in a dog by crushing the pancreas. A hematoma developed and subsequently 100 mls of milky fluid collected in the lesser sac. In 1957 Jackson and Howard were unsuccessful in producing a single cyst in 38 dogs. They found that ligation of the pancreatice ducts led to fibrosis, that incisions in the pancreatic ducts were sealed by omentum, that crushing produced scarring, as did injection of blood and pancreatic juice or bile into pancreas of pancreatic ducts. Karlan, McPherson and Watman in 1958 reported production of a cystlike structure by wrapping the tail of the pancreas in omentum following complete transection of the pancreas and partial occlusion of pancreatic ducts. Omental encapsulation was presumably intended to simulate the confining features of the lesser peritoneal sac. Warren, Marsh and Muller produced a fibrous encapsulation of a polyethylene bag embedded in the peritoneal cavity adjacent to the pancreas. None of these experiments is very conclusive.

The following is the current concept of the etiology and pathogenesis of the pseudocyst. The most common cause in the human is pancreatitis which is an antecedent factor in 65-75%. A cyst may develop following a single episode of acute pancreatitis or in a patient with chronic relapsing pancreatitis. With damage to the pancreatic acini, pancreatic enzymes chiefly lipase and trypsin are released into tissues and activated. They cause further digestion and necrosis with sloughing of pancreatic tissue and accumulation of blood and pancreatic juice in the area of necrosis. Rupture into the lesser sac produces the intense inflammatory reaction of chemical peritonitis which incites the proliferation of fibrous connective tissue which makes up the major part of the cyst wall. The foramen of Winslow which is normally surrounded by loose connective tissue is completely obliterated by the inflammation and fibrosis and a well demarcated cyst is formed. The association of gallstones with pseudocysts has been noted for many years but current thought tends to the theory that when gallstones are present, there is also pancreatitis and the latter initiates the necrotic process that leads to cyst development. Trauma is the second most common cause particularly in the 0-20 age group. The pancreas unprotected by a true enveloping capsule lies at right angles to the unyielding vertebral column and is therefore

very vulnerable to trauma. Perforating injuries are usually explored and the pancreatic wound drained thereby permitting the escape of pancreatic juice. Blunt trauma however may compress the pancreas against the vertebral column leading to the escape of pancreatic juice and blood into the lesser sac exciting the same kind of inflammatory reaction and fibrosis described earlier. Other types of trauma reported to have preceded the development of a pseudocyst are gastric and biliary surgery, partial pancreatectomy, splenectomy, needle biopsy of the pancreas and palpation of the pancreas at laparotomy. Pseudocysts may or may not have a permanent communication with the pancreatic duct system from which secretion is continuously poured into the sac distending and enlarging it. A pseudocyst, then, is the result of a local chemical peritonitis resulting from the release of pancreatic ferments and blood from the substance of the pancreas by inflammation or trauma.

Pathology

Pseudocysts can present in a wide variety of locations. They may be situated within the pancreas but usually they are found adjacent to the pancreas in the lesser sac, so that the wall of the cyst is formed posteriorly by the body and tail of the pancreas with peritoneum covering them, anteriorly and superiorly by lesser omental structures and anteriorly and inferiorly by the posterior wall of stomach, gastrocolic omentum and transverse colon. It may point through the gastrohepatic ligament displacing the stomach inferiorly or through the gastrocolic omentum displacing the stomach superiorly. The fluid collection may extend downward behind the posterior peritoneum and appear in the LLQ or ascend into the inferior mediastinum. Cysts may even become incorporated into the muscular wall of stomach, colon or duodenum.

Pseudocysts vary in size from a few cm. to 35-40cm, may contain as much as 4 L of fluid and are usually unilocular. They appear as rounded edematous indurated cystic masses surrounded by a fibrous capsule of varying thickness which is usually densely adherent to surrounding structures. There is by definition no epithelial lining, but there is often an intense inflammatory reaction on the wall. Fluid in the cyst is generally turbid. It may be brown from old blood, red with frank flood, milky, bile stained or purulent. It may or may not contain pancreatic secretions, but usually amylase is present in higher concentrations than are found in serum. In addition, blood cells, epithelial cells, necrotic pancreatic tissue and cholesterol may be found.

Clinical Presentation

Pancreatic pseudocyst has frequently been a source of diagnostic confusion and has often escaped consideration in the preoperative period. The proximity of the cyst to many organs which are the site of common disease processes justifies this to some extent but if the clinical manifestations of pseudocyst are kept in mind, a tentative diagnosis can be made preoperatively in many cases. As mentioned before, the most common antecedent is a history of pancreatitis. While a cyst may develop during the first attack, there are usually repeated attacks suggestive of pancreatitis before the development or at least the recognition of a cyst. 5-10% of patients with chronic pancreatitis eventually have a pseudocyst. Frequently there is also a history of cholecystitis. Where trauma is the initiating factor, a cyst may not be recognized for intervals from weeks to years. Not infrequently there is nothing in the history to suggest an apparent cause for the development of pseudocyst.

Pain is the commonest symptom being present in 80-95% of most series. Probably pancreatitis is one cause of pain in many cases as the character and location of the pain are typical of pancreatitis. The pain is usually epigastric occasionally radiating through to the back, but there may be RUQ, LUQ, umbilical or diffuse back pain. The pain may be very severe requiring hypodermic injection of very mild. It is usually constant but may be colicky. It varies in duration from a few hours to a week and in occurrence from once or twice a year to one very acute episode. When pain subsides in many cases there is a residual soreness for several days. Nausea and vomiting are perhaps the next most common symptom occurring in 20-60% of various series of reported cases. Dyspepsia with excessive gas and bloating, constipation or diarrhoea may also occur. Jaundice of the obstructive type occurs occasionally, usually as a result of extrinsic pressure on the CBD, but it may be the result of gallstones or pancreatitis. The jaundice may fluctuate. The most common systemic symptom is recent weight loss seen in up to 50% of cases. Fatigue, chills and fever are also reported.

On physical examination, up to 90% of patients have a palpable mass, and not infrequently it is sufficiently large to be noticed by the patient. The mass may be present for a short time or several years. Usually it is situated in the epigastric region but occasionally it has been reported in the lower abdomen or pelvis. It may occupy most of the abdominal cavity. It is round and smooth and usually feels cystic although it is generally too tense for a fluid thrill to be appreciated. A change in size often occurs presumably due to partial drainage into pancreatic ducts, and even the patient may note that the mass changes in size and consistency. Between attacks of pain, the mass may entirely disappear. Its mobility depends on the degree of fixation to surrounding structures so that some are slightly mobile and move with respiration while the majority are fixed. Although these lesions are the result of trauma or inflammation, tenderness is not common. When the cyst is firm, nontender and fixed, it is suggestive of a malignant neoplasm, and the suggestion may be enhanced if there is associated jaundice and loss of weight. Up to 10% of

reported cases have hydrothorax a few of which have a high amylase in the fluid. The hydrothorax tends to clear after treatment of the cyst. Other rare findings are chylothorax, ascites, portal cirrhosis, and edema.

Laboratory Findings

Laboratory findings are not of much help in the diagnosis of pancreatic cyst. Diabetes mellitus is diagnosed in 5-20%, probably a result of extensive and long-standing inflammation in the pancreas. Serum amylase values are more often elevated than lipase levels, but even these are not constant enough to be of diagnostic aid. A greater percentage of elevated values may be found in acute episodes of pain. Occasionally excessive fat and N are found in stools—evidence of insufficient external pancreatic secretion. Leukocytosis may be present if the inflammatory process is acute. Rarely, hypersplenism resulting from splenic vein compression may produce pancytopenia.

X-ray of the abdomen is one of the most valuable diagnostic aids. On plain film a soft tissue mass may be seen, usually smooth and spherical or hemispherical. Pancreatic calcification is found in up to 20% of patients. Cysts can produce extreme indentation of any hollow viscus they approximate. The upper GI series is frequently quite characteristic. The cyst is usually behind the stomach and between stomach and transverse colon so that the stomach is displaced with indentation of the greater or lesser curvature. The duodenal loop may be widened suggesting a head of pancreas, the left kidney may be displaced, or the left diaphragm elevated. The barium enema shows inferior displacement of the colon. Occasionally the cyst may distort the IVP. A non-functioning gallbladder and stones are not uncommon. The chest X-ray may show hydrothorax.

The differential diagnosis consists of other cystic enlargements in the abdomen and intraabdominal and retroperitoneal tumours as well as pancreatitis, cholycystitis and peptic ulcer.

To summarize, the diagnosis depends on history, physical and X-ray findings. It is one of exclusion of the more common abdominal lesions and is rarely made definitely preoperatively. A strong presumptive diagnosis can be made on a history of recurrent pancreatitis or blunt abdominal trauma presenting with a round mass in the upper abdomen particularly if the X-ray shows displacement of the stomach and colon.

Treatment

Virtually all cases of suspected pancreatic cyst should undergo operation. In many cases, symptoms warrant exploration, in others the finding of a mass will be an indication for surgery to rule out more serious lesions of pancreas or adjacent organs. Even if a diagnosis of cyst of pancreas can be made preoperatively with some certainty, it is impossible to determine that it is not a cystadenoca. Benign asymptomatic cysts may produce complications such as obstructive jaundice, infection, hemorrhage or rupture which carry a high morbidity and mortality. Most of the interest in pancreatic pseudocysts centres on the controversy concerning the best method of treatment. These may be summarized as follows:

1) excision

2) pancreatectomy

3) drainage
   a. external—marsupialization
      —catheter
   b. internal—anastomosis of the cyst ot an adjacent hollow viscus

4) sphincterotomy

None of these methods of treatment are new. The first attack on a pancreatic cyst was described in 1865. The cyst was punctured in the belief that it was originating from the liver, and the patient succombed to peritonitis. 1866 saw the successful drainage of a cyst, and in 1881 a pancreatic cyst was excised. In 1882 Gussenbauer sutured the parietal peritoneum to the skin and then the walls of the cyst to the parietal peritoneum. This technique of marsupialization subsequently became and has remained a standard surgical procedure. Removal of calculi and the technique of sphincterotomy were described in a book published in 1901. In 1923 Jedlicka managed a cyst by means of drainage into the stomach.

The first principle of treatment is that it is always necessary to biopsy the wall of the cyst to rule out the presence of malignancy.

Excision is the surgical treatment of choice but is applicable in very few instances chiefly in cases of small cysts in the distal segment with minimal surrounding inflammation. Most cysts are too large and too densely adherent to surrounding structures for excision to be technically feasible. Pancreatic resection is a difficult procedure with a high morbidity and mortality rate and is seldom justified for the treatment of pseudocyst.

When complete removal of the cyst is impossible, it is necessary to provide drainage so that the cyst collapses gradually, and the cavity is obliterated. External drainage is the simplest of all procedures and can be used on poor risk patients or those in whom the cyst wall is inflammed and not sufficiently firm to hold sutures well. The cyst can be drained with any of a number of catherers or can be sutured to the parietal peritoneum and skin. The disadvantages of external drainage are:

1) prolonged drainage, an average of 5-6 months in most cases and up to 5 years not infrequently. Drainage is very prolonged if there is a communication with the duct system and a second operation is frequently necessary

2) fistula formation
3) excoriaton of skin
4) electrolyte imbalance from fluid loss
5) secondary infection

Internal drainage has gained popularity in the last 5 years because it returns fluid secreted into the cyst to the gi tract and eliminates the nuisance to the patient of a drainage wound. In general the cyst is anastomosed to whichever hollow structure it is most densely adherent to. The two most common methods are anastomosis of the cyst to the stomach and anastomosis to the jejnum. Since most cysts are densely adherent to the posterior wall of the stomach, cystogastrostomy is quite popular. It is stated that there is reflux of gastric contents to the pouch but barium studies have shown that this takes place for the first 2-3 weeks only and emptying occurs promptly so that peritonitis and pancreatitis are rare complications. Furthermore it appears that the cystic fluid does not lower gastric acidity, and ulceration of the stomach mucosa by pancreatic juice is rarely reported. Anastomosis to the jejunum is carried out by a Roux en Y loop. The jejunum is divided 6" distal to the lig. of Treitz and the distal end of jejunum is joined to the most dependent portion of the cyst. Gastrointestinal continuity is re-established by jejeunojejeunostomy 16" distal to the anastomosis with the cyst. By this means reflux of gi contents into the cyst is prevented since the cyst is anastomosed to a defunctioning loop of bowel and cyst contents are drained into the jejunum in a physiological manner. When the cyst cavity is obliterated, the defunctioning loop remains as a blind pouch. The disadvantages of internal drainage are:

1) it is an extensive operation which poor risk patients cannot withstand

2) the stoma may close prematurely before the cyst cavity is obliterated leading to recurrence of the cyst. Some authorities feel that whatever the method of drainage, a sphincterotomy, in which the sphincter of Oddi is incised, should be done as well particularly when a communication with the duct system can be demonstrated to lower the intraductal pressure and prevent continued reflux into the cyst cavity and the pancreas producing recurrent pancreatitis and cyst.

SUMMARY

Pancreatic pseudocysts are collections of fluid enclosed by fibrous tissue found adjacent to the pancreas following pancreatitis or blunt trauma. The diagnosis should always be suspected when a patient with a suitable history presents with epigastric pain and an abdominal mass. Barium studies of the gi tract are the most helpful diagnostic tool. Operation is almost always necessary to relieve symptoms and to obtain a biopsy to rule out the presence of ca which often gives similar findings. Excision is rarely feasible and therefore the cyst must be drained either externally or internally. Choice of treatment must be based on a consideration of the state of the patient, the nature of the cyst wall and the location and size of the cyst. Internal drainage is an increasingly popular method of treatment.

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Diabetes Mellitus - Current Concepts

Michael Bach 6T7

The purpose of this paper is an attempt to review current concepts concerning the metabolic disturbances in diabetes mellitus, especially in their relation to the development of the clinical syndrome which results. The efficacy of current therapy in the light of this knowledge will be evaluated. It must be recognized that the field of diabetes is too immense to consider all aspects in this review, and thus at the expense of being complete, certain topics will be omitted or just briefly touched on.

Until a few years ago, it was thought that "Idiopathic" Diabetes was caused by a primary failure of the pancreas to secrete insulin. Since it was found that by injecting insulin into diabetic patients, the hyperglycemia and glycosuria were ameliorated. However, in recent years, many workers have realized that in the early stages of the disease, especially in the maturity onset type, the level of insulin in the blood is normal or sometimes even raised in amount.[1] It was also discovered that on electron microscopic examination of the granules in the beta cells of the Islets (thought to be the storage form of insulin),[2] there were only nonspecific abnormalities demonstrable in these cells. In at least 25% of cases, the islets were, to all extents and purposes, normal.

Thus investigators were spurred on to look more carefully at the various aspects of insulin action, and numerous theories and findings flooded the literature. Renold, on assaying insulin levels in maturity onset diabetics after glucose loading tests, discovered that these people did secrete insulin. However, the rate of rise in the blood was extremely retarded and when the level did increase, it rose to a peak much greater than in normal people.[3] This suggested to him that perhaps there were sites where there was either a failure of insulin release in response to normal physiological stimuli or failure of insulin to act on the cells, and a consideration of all possible anatomical sites at which blocking of insulin may be achieved was undertaken.

Current work is now attempting to evaluate each area in this problem in the hope of detecting some abnormality of structure or function.

ETIOLOGIC SITES — from pancreas to cell

1. Impaired reception of stimulus at the beta cells
2. Impaired release of insulin from beta cells
   a) Autoimmune mechanism
   b) Deposition of blocking substance
   c) Pancreatic insufficiency
3. Blood:
   a) Conversion of insulin to a bound inactive form
   b) Development of insulin antagonists
   c) Influence of free fatty acids on insulin control
   d) Role of Growth Hormone in insulin inhibition
4. Vessel wall—alteration of basement membrane preventing egress of insulin
5. Tissues—insensitivity to insulin
   a) Cell membrane blockers?
   b) Altered membranes?

Intensive work in these areas has been done in the past few years, and a clarification of some of these theories may be helpful.

No current etiological theory is complete without its autoimmune component. Much interest was generated in this direction by two observations. The first was that made in electron microscopic studies of pancreatic islet lesions in diabetics. It had been known for a long time from light microscopy that hyalinization of the islets was present in some 25% of diabetics (and in some "normal" individuals). This lesion was seen under the electron microscope as masses of interlacing small fibrils closely resembling the structure of a myloid, and appearing between, not in, the basement membranes. The lesion was also thought to be different from the material seen in vessels of diabetics which has been shown to be thickened basement membrane. There is thus the suggestion that the substance in the islets may represent either a binding protein associated with insulin,[4] or the site of an antigen-antibody reaction impeding insulin release into the blood.[5] [6]

The second observation was the discovery of insulin antibodies in the sera of diabetic patients. Although it has been realized that the antibodies are probably iatrogenically induced by parenteral hog or beef insulin injections, some workers feel that the islets are situated in a similar anatomic position to that of the thyroid acini; i.e. they are virtually isolated from the general circulation. They feel that because insulin circulates in such small quantities, the newborn has no chance of developing immune tolerance to it, and if it is released in larger quantities later by some mechanism, then autoantibodies may be developed against it.[7] One may consider this theory in passing, but there is no evidence at the present time to substantiate the autoimmune features.

Primary pancreatic insufficiency must still be considered a possibility since many diabetics do demonstrate a very low or even absent insulin level in the blood.

A number of researchers have found that insulin circulates in the plasma in two forms; an active unbound form and an inactive bound form. The two forms have been characterized and found to have different physicochemical, biological, and immunological characteristics. There seems to be a biochemical mechanism regulating the transfer of the inactive form to the active form in times of metabolic need for insulin. It is interesting to note that when the blood of newly discovered non-insulin dependent maturity-onset diabetics was assayed, it showed that there was a much higher ratio of bound to free insulin than that of the non-diabetic controls, even though hyperglycemia was present. The assumption here is that there is either a high rate of activity of "complexing enzyme" or a slowed rate of breakdown of the complex.[8] Since the tissues do not receive their insulin, blood sugar increases, and the sustained pancreatic stimulus leads eventually to exhaustion atropy of the gland.

This theory seemed quite attractive until several workers questioned whether there actually existed such an entity as "bound" insulin, and further work is now being done to carefully identify this complexed protein.

Vallance-Owen and workers have found that in diabetics and prediabetics, there is a substance which migrates electrophoretically with albumin which they have called Synalbumin. It has been identified as the B chain of insulin resulting from degradation of the whole molecule. Synalbumin antagonizes insulin, possibly by competitive inhibition at the cell membrane, since this action can be overcome by adding greater quantities of insulin to sera where synalbumin is present.[9] No such antagonist has as yet been identified in normal subjects or in subjects with secondary diabetes. It is of further interest that this antagonist disappears in animals which have been hypophysectomized.

Vallance-Owen thus postulates a disturbance in balance between antagonists mediated via the pituitary-adrenal axis and insulin produced by the pancreas. With increased activity of the pituitary such as in growth, stress, and pregnancy, there is increased synalbumin production which may tip the precarious balance in a diabetic. (Such states are recognized today as possible factors precipitating the onset of diabetes in people who have prediabetes or chemical diabetes.)

It was also found that synalbumin has no antagonism to insulin's effect on adipose tissue although it is marked in muscle. This may explain the obesity of maturity onset diabetes as a shunting of glucose into adipose tissue with resulting increase in fat synthesis. Also, because synalbumin is believed to cross the placenta, a form of intrauterine antagonism may explain the fat flabby stillbirths with hypertrophied islets that are characteristic in some prediabetic and diabetic mothers.

This elaborate theory has been recently challenged on chemical grounds by workers who feel that synalbumin does not really exist—that it is simply an artefact of the biochemical purification process involved in the experiments. They have found no antagonism in sera before the albumin fraction has been separated, and also found no antagonism by injecting the B chain of insulin directly. Nevertheless, some substance inhibits glucose uptake of the diaphragm *in vitro* and the fact still remains that the "synalbumin" level appears higher in diabetics and interestingly enough in families with prediabetes as well. To date, there has been no resolution of this fascinating issue.

In 1963, Randle, at Cambridge, proposed consideration of the important role of fatty acids in the aetiology of diabetes. He proposed that a high level of fatty acids, resulting in increased formation of Acetyl Co-A via the Lynen Spiral, leads to an overload and thus backup in the glycolytic sequence which extends to Glucose-6-Phosphate. This substance gradually increases in concentration and inhibits the hexokinase responsible for phosphorylation of glucose. Glucose thus builds up in the blood and is unaffected by insulin levels. Many people feel this is an excellent explanation of the role of fatty acids; however, Randle goes one step further and postulates that this increase in fatty acids is the primary defect, and that possibly Growth Hormone is the agent which initially causes these high levels of fatty acids.[10 11 12] This, however, is only an attractive hypothesis requiring validation in human prediabetes. It must be considered that the high early levels of fatty acids[10] which were measured are so variable and altered by so many factors, that when all controls and necessary factors are taken into account, then, and only then, can some conclusion be drawn concerning their role in this disease.

The role of Growth Hormone and pituitary-insulin antagonism has been debated for a long time because it had been recognized that hypophysectomy will ameliorate diabetes caused by pancreatectomy. It was also considered that Growth Hormone(GH), possibly in conjunction with ACTH, was responsible for the production of a substance in the B_1-lipoprotein fraction which inhibited the action of insulin.[13] This has not been able to be verified. In Randle's studies, GH was elevated in seven out of seven untreated diabetics. It has also been considered to play a role in the development of diabetes because prediabetic females are known to deliver large babies and exhibit hyperlactation, both functions being regulated by GH.[14] Newer assays however, have found that GH in pregnant females is not elevated, but, there is an elevation of a placental hormone Chorionic Growth Hormone—Prolactin secreted by the syncytiotrophioblast which itself may be diabetogenic.[15] The fat and large babies usually have islet hyperplasia and their obesity and overgrowth may be a result of insulin—infant GH synergism acting on adipose tissue and skeletal development as well.

The problem that one runs into here is that the GH level may be affected by so many variables that it is

really difficult to obtain a true base level for comparison. The current status of GH is undecided, but definitive studies are important, especially since one of the current modes of treatment for severe malignant retinitis proliferans is hypophysectomy, a treatment which seems to help slow down the progressive retinal changes. One may also ask why, if GH is an important factor, do not all acromegalics suffer from diabetes?

One of the first pathological changes seen especially in the kidney and skin, but also in other organs, is a thickening of the basement membrane. Electron microscopic examination of blood vessels reveals widening, with an increase in a PAS positive staining material. This thickening might possibly prevent egress of insulin from the blood to the peripheral tissues.

These theories were presented to illustrate current ideas of interest in defining the primary abnormality in idiopathic Diabetes Mellitus. One may see how confusing and complex this field is, and this will perhaps emphasize where we stand in trying to control or prevent appearance of this disease and in trying to define what precisely the underlying pathological process is.

What are we attempting to treat? Perhaps an elucidation of the pathophysiology and clinical presentation of the disease is in order so that at least the fundamental biochemical changes may be noted and their correlation, or lack of correlation with the lesions defined.

FUNCTIONS OF INSULIN

1. Increases lipogenesis.
2. Increases glucose entry into cells:
   (a) Liver glucokinase activity enhanced
   (b) Muscle and adipose tissue membrane permeability increased.
3. Increases amino acid uptake by muscle and increases protein synthesis.

A well defined pattern may be observed when insulin deficiency or lack of insulin effectiveness is examined. Glucose fails to be taken up by muscle and adipose tissue and is phosphorylated in the liver cells only in very small amounts. There is then accumulation of glucose in the bloodstream-*hyperglycaemia.* Increased glucose concentration in the blood increases the plasma osmolarity, drawing fluid out from the intercellular compartment—*intercellular dehydration.* The glucose acts as an osmotic diuretic carrying out water with it in the urine—*polyuria.* Decreased intracellular and extracellular fluid volume stimulates the hypothalamic thirst centre—*polydypsia.* With no insulin, there is increased lipolysis, resulting in raised non-esterified fatty acid (NEFA) levels in the blood. These NEFA'S converge on the liver—*fatty liver.* Total plasma lipid levels may increase—*lipemia.* There is also an elevation in the cholesterol fraction probably due to increased synthesis as a result of the increase in acetyl Co-A levels. With prolonged cholesterolemia, one may get cholesterol deposition in the skin, especially the skin creases and eyelids—*Xanthoma Diabeticorum.* Gluconeogenesis is stimulated, with increased conversion of amino acids via the four carbon dicarboxylic acid shunt to glucose resulting in increased protein catabolism—*weight loss.* There is also a great stimulus in appetite due to caloric losses—*polyphagia.* Accompanying these symptoms and signs are constitutional changes such as malaise, fatigue, and weakness attributable to the great metabolic "drain".

With the disease uncontrolled there is further progression. The liver utilizes the fatty acids formed to generate the energy it is not obtaining via glucose utilization. Increased amounts of acetoacetyl-CoA are formed and accumulate because the Krebs cycle has been interrupted in order to enhance gluconeogenesis. This results in deficiency of oxaloacetic acid needed to form citric acid with acetyl CoA. Acetoacetyl-CoA is split to acetoacetic acid via the liver specific enzyme, Deacylase, and with some alternate conversion to either B-hydroxybutyric acid or acetone, diffuses into the bloodstream—*ketonemia.* Muscle can usually handle the normal amounts of ketones by reconverting them to acetyl-CoA via the succinyl-CoA transferase or specific thiokinase mechanisms, but these enzyme systems are overloaded by the excess ketones which accumulate, and since the renal threshold for ketones is very low, they pass into the urine—*ketonuria.* These strong anions drag cations with them, first ammonium, then sodium and potassium so that the body becomes depleted of fluid and electrolytes—*dehydration;* hydrogen ions in turn accumulate—*acidosis.* Chlorides, magnesium, calcium, and nearly 20% of the total body potassium may be lost. The body attempts to compensate for this acidosis by getting rid of carbon dioxide and acetone via the lungs with deep rapid respirations—*Kussmaul hyperpnea.* Either compensation is achieved, with buffers, lungs, and kidneys holding their own, or decompensation ensues due to vomiting (one effect of acidosis), or failure to receive insulin. There is increasing fluid loss resulting in decreased renal flow with increasing acidosis leading to coma and possibly death.

The varied physiological mechanisms which are disturbed may lead to a symptom complex of protean manifestations; however, as previously discussed, since the carbohydrate disturbance is not the first change noted in the diabetic state, classification of the clinical picture has changed and must now take into account new factors in defining the disease entity.

Three major divisions are now considered:

1. Prediabetes

This is the period of life where the individual exhibits no abnormality of carbohydrate metabolism, but will eventually develop diabetes. It is defined in terms of his genetic history, i.e. blood relatives or if he is an

identical twin then he will develop diabetes.[16] Mothers who deliver babies over 10 pounds in weight are considered suspect. The definition of what constitutes a diabetic state is now incorporating many more factors unearthed by recent investigations.

2. Chemical Diabetes

This stage is determined chiefly by the use of the glucose tolerance test which for the present time is considered the "sine qua non" diagnostic test for diabetes.[17] Other tests, such as the fasting blood sugar, post-prandial blood sugar, and more esoteric tests such as the cortisone-provocative test, are all useful in helping point to the carbohydrate abnormality.

3. Clinical Diabetes

This is the well recognized state where varied signs and symptoms are manifested. It may be advantageous at this point to outline some of the main clinical features in order to comment on current thinking regarding their etiology and possible effects of treatment.

A. *Acute Stage*[18]—commonly seen in the newly discovered brittle juvenile diabetic or in an older diabetic who has incurred some recent infection. The clinical picture is that described under the complex of ketoacidosis.

B. *Subacute stage*—here the findings are generally non-specific, with the patient presenting with pyodermia, pruritis, blurred vision, perigenital moniliasis, etc.

C. *Chronic Stage*—in this stage, the major symptoms are seen, but where previously they were considered to be complications of the disease, they are now thought of as integral and genetically determined manifestations. In considering these stages, one generally sees four major areas of involvment.

1. Vascular System:

a) Atherosclerosis
b) Monckeberg's sclerosis
c) Arteriolosclerosis

These need no further elaboration other than to mention that diabetics are found to have a high incidence of degenerative or occlusive vascular disease with all their accompanying complications such as coronary thrombosis, cerebrovascular accidents, peripheral gangrene, etc.

2. Ocular System:

a) Cataract formation
b) Retinopathy
   i) microaneurysms and hemorrhages
   ii) venular dilatation and beading
   iii) waxy exudates
   iv) neovascular proliferation
   v) central fibrous connective tissue proliferations
   vi) retinal detachment

3. Urinary System:

a) Pyelonephritis—acute and chronic
b) Papillitis necroticans
c) Urinary tract infections
d) Diabetic nephropathy
   i) hypertension
   ii) nephrotic syndrome ultimately leading to
   iii) chronic renal failure

The kidneys characteristically exhibit the changes of intercapillary glomerulosclerosis or Kimmelstiel-Wilson lesions. A patient with renal disease and exhibiting diabetic retinopathy will usually have the K-W nephropathy.

4. Neurological System:

a) Peripheral nerves

i) symmetrical polyneuropathy—the most common neurological disorder in diabetics usually affecting the lower extremities.

ii) mononeuropathy, or mononeuropathy multiplex—it may involve any nerve, motor, sensory, or mixed. Commonly it involves the sciatić and ulnar nerves.

iii) radiculopathy — lancinating pain. Sensory dermatome and reflex changes.

iv) cranial neuropathy—3rd and 6th nerves are the most common. Argyll-Robertson pupils. Optic neuritis. Every cranial nerve, except 1 and 12, have been reported involved.

v) autonomic system:

1. sympathectomy type—orthostatic hypotension, syncope.
2. autonomic activation — sweating, pale, cold extremities.
3. gastrointestinal—diarrhoea. Gastric atony with abdominal pain, nausea vomiting. Constipation.
4. genito-urinary — impotence. Atonic bladder. Urinary incontinence.

Charcot's neuropathic joints and neuropathic ulcers are also found as results of peripheral nerve lesions.

b) Spinal Cord

i) amyotrophy—bilateral weakness of pelvic or shoulder girdle associated with atrophy.

ii) diabetic pseudotabes — posterior column involvement with diffuse pain and weakness and wasting of proximal muscle groups.

iii) acute vascular syndrome — myelomalacia. Seen as an acute spinal accident such as anterior spinal artery thrombosis.

c) Cerebrum

i) cerebrovascular accidents and chronic cerebrovascular disease

ii) hypoglycaemia

iii) diabetic coma

iv) meningitis—mucormycosis especially.

d) Neurological Abnormalities in Newborn

A high percentage of neurological abnormalities are found in babies born of diabetic mothers. Hydrocephalus, meningocoele, mental retardation, deafness are but a few of those documented which occur more frequently in diabetics.[19]

It may be of interest to note that the neurological disorders seem to be unrelated to the severity of glucose intolerance; that is, to the quantity of insulin required by a diabetic for blood sugar stabilization. Relatively "mild" diabetics are found to have just as severe and just as many of the neurological changes as "severe" diabetics.[20] The duration of the diabetic state has also no close relation to the development of the lesions; in fact, some of the presenting symptoms that a newly-discovered diabetic may exhibit are neurological ones. New work on the subject of vascular disease in diabetes has suggested that the basic cause of the neuropathology is a microangiopathy affecting the vasa nervorum.[21] No conclusion has yet been reached.

Where previously the different clinical states were considered to be varying manifestations of diabetes, current work has concentrated on attempting to isolate and define a single pathologic change common to all lesions. Recent electron microscopic studies have focused on a thickening of the basement membranes in the vasculature of various organs. An ingenious experiment involving histologic examination of retinal vessels has suggested that the microaneurysm formation in the retina is a result of shunting of blood into a capillary with weakened walls—the weakening being due to a defective wall possibly because of loss intramural cells which are normally responsible for vessel wall integrity.[22] These cells have also been found to be absent in the kidney. Studies in prediabetics has confirmed the presence of basement membrane thickening before the onset of classical retinopathy. Daysog reported 100% of the prediabetics he studied as showing basement membrane thickening, and 50% demonstrating K-W lesions in renal biopsies.[23] In considering what the cause of this thickening could be, and understanding that normal capillary basement membrane is a form of glycoprotein, Spiro has postulated a rerouting of biosynthetic pathways. He has found that the biosynthesis of glycoprotein is insulin-dependent, and reasons that in diabetes the glucose normally passing into the Embden-Meyerhof pathway is shunted into the glycoprotein pathway with resulting increased deposition in the vessel walls.[24] What relation this thickening has to the development of lesions and symptoms has yet to be clarified.

TREATMENT

The question of etiology remains unanswered. It is true that at the present time, we are treating merely a blood sugar figure in the blood stream and not truly understanding how this will affect the development of the "complications". Uncontrolled diabetes is considered now to be an unbalanced and unnatural metabolic state somewhat analogous to a non-specific infection taking its toll on body constituents, rather than simply a state where high blood sugar levels have a deleterious effect on the various organ systems. The attempt to keep the diabetic controlled is an attempt to keep him in as "physiological" a state as possible recognizing all the while that he will probably develop his "genetically determined complications" but will perhaps be in a better state to handle them.

One may appreciate the basic aim of therapy if it is realized how one's insulin is regulated normally. In a nondiabetic, the intake of food determines the amount of insulin secreted by the pancreas, and thus insulin is subservient to body needs and food intake. When the pancreas can no longer respond to a physiological stimulus, or when insulin itself is no longer effective, then what we have to do is supply insulin and regulate our food intake accordingly. This involves regular and frequent meals (if necessary) and a steady, limited, and balanced caloric intake which is thus able to be well metabolized by a standard and regular dose of insulin and which does not result in any rebound Somogyi effect. It is well recognized that some elderly diabetics may be stabilized simply by a loss of weight and well controlled diet; others may be regulated by the taking of the pancreas-stimulating sulphonylureas, but the basic concept of stabilization and regulation continues to hold true.

With more awareness and more sensitive detection devices, diabetes is being diagnosed more frequently today. The problem of determining where the primary defect lies, and what happens once this defect is manifested, seems now to be of prime importance in attempting to come to grips with this disease. Diabetics today, thanks to insulin, are at least able to live somewhat normal lives and perform adequately in society. One must realize that although the immediate metabolic abnormalities are controllable, there is as yet no way of predicting or controlling the onset of the complications though it is known that in most cases, the longer the diabetic state exists, the greater are the chances of complications appearing. This today poses the greatest challenge to the physician and researchers—for where before the diabetic died early in coma, today he lives longer and dies with gangrene, nephropathy and cardiovascular disease. Thus elucidation of the etiology may thwart the dreaded complications by prevention rather than by control.

SUMMARY

Newer research work in the field of diabetes has been reviewed and current concepts regarding the etiology of the disease are presented.

ACKNOWLEDGEMENT

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G. S. BURTON, M.D.C.M., *Medical Superintendent.*

Robert Liston

"It is of the utmost importance to attend to the state of the patient's mind and feelings. He ought not to be kept in suspense, but encouraged and assured; and his apprehensions must be allayed. If this cannot be effected—if he is dejected and despondent—talks of the great risk, and of the certainty of his dying, it is better that the operation be abandoned or at least delayed. If, on the contrary, he is confident of the benefit to be ganed from his own fortitude then there should be no delay".

The above was spoken by a London surgeon named Robert Liston, thus demonstrating the great interest he had in the welfare of his patients, even though he spent most of his life practicing daring surgery without the benefit of anaesthetic drugs. It is not surprising then, that this same man was the first in his country to seize the opportunity to try using ether inhalation as a means of destroying the great pain associated with operative procedures.

Robert Liston was born in 1794 the son of a minister. He was educated mainly by his father and at the age of fourteen entered the University of Edinburgh. At the age of sixteen he became an assistant to Dr. John Barclay who, in his lectures on anatomy, passed on to his pupils respect and appreciation for good surgery. Liston's hospital training was acquired at the Royal Infirmary of Edinburgh and the London Hospital. By the age of twenty-four he was a member of the Royal College of Surgeons of England and the Edinburgh College of Surgeons.

Right from the start of his career Robert Liston could be counted on for the unusual. He had unusual technical skill but also unusual methods of practice. Shortly after accepting a post at the Royal Infirmary his privileges were revoked for five years. He was accused of enticing and then operating upon patients who were denied surgery at the Infirmary. This hardship did not seem to hamper his career. In 1827 the ban was removed, and he was, at the same time, appointed to a senior surgical post. The following year he was awarded the Professorship of clinical surgery in the newly founded University of London Hospital.

Liston was not a scientific surgeon, rather his reputation was gained through dedication to teaching, and most important in his era, complete self assurance, great dexterity and lightning speed in major surgical interventions. He admitted the hazards in operative procedures, but affirmed a belief in the surgeon's capacity to be of greater help to the patient in need of surgery than any conservative course. This idea is stressed in his "Introduction to Practical Surgery" where he wrote the following.

"To treat surgical diseases as they ought to be treated, the practitioner must be thoroughly acquainted with the healthy and morbid structure; he must also have a mind vigorous and firm from nature, well instructed in the best precedents, and matured by observation. With knowledge and confidence derived from experience he will perform swiftly. Such operations as are indispensable for the removal of pain and deformity or for the preservation of life.

Were the recommendations given above better followed, we should have presented to us fewer of those scenes shocking to humanity, which have been so well described by one of the most interesting writers on surgery. The operators are represented as agitated, miserable, trembling in the midst of difficulties, feeling in the wound for things the position of which they had not understood, turning round to their friends for that support which should come from written, holding consultations amidst the cries of the patient, or even retiring to consult about his case while he was bleeding, in great pain, and awful expectation."

Robert Liston's description of amputation at the hip joint, in the period immediately preceeding the discovery of ether for anaesthesia, is indeed graphic. It demonstrates the fine technique and careful attention to detail which characterized his work. The report, published in "Elements of Surgery" is as follows.

"Amputation at the hip joint is deservedly ranked amongst the most formidable operations in surgery. It ought, therefore, never to be performed but as a last and necessitous resource for the salvation of life. The patient is placed recumbent upon a firm table his nates resting on, or rather projecting a little over the front edge. The sound limb is separated from the one to be removed, and held aside firmly by the assistant. Or it is secured to the foot of the table by a towel, the necessity for an additional assistant being thus done away with, and more freedom in his movements being afforded to the operator. The other limb is supported by an experienced and intelligent assistant, who understands and is able to perform the movements to facilitate the different steps of the operation. The compression is intrusted also to an experienced and steady assistant, who, standing by the patient's side, presses firmly with one or both thumbs on the femoral artery where it passes over the pubes; and in this more than any other operation, should the pressure be delayed till the instant of incision, for otherwise the blood lost

in the limb will be immense. Transfixion, by a knife proportioned to the dimerisions of the limb, is made horizontally, the instrument being passed in a somewhat semicircular direction, so as to include as much of the soft parts as possible; an anterior flap is made by cutting downwards. During the passage of the knife across the joint, the assistant rotates the limb a little so as to facilitate the bringing of the instrument out with its point well inwards; in the left limb the rotation will be inwards, in the right outwards. After formation of the flap, the assistant abducts forcibly, and presses downwards; the joint is opened, the round ligament cut, the capsule divided, and the blade of the knife placed behind the head of the bone and the large trochanter; the posterior flap is then made very rapidly. After transfixion for the superior flap, and when the sawing motion downwards has advanced but a little way, the compressing assistant shifts his hands into the incision immediately behind the back of the knife, and so obtains a firm grasp of the femoral previous to its division. He retains this hold, at the same time retracting the flap, during the rest of the operation. As soon as the limb has been separated, the surgeon secures the vessels on the posterior flap, partly by compression with a large sponge, partly with his fingers, and ligatures are applied as quickly as possible. The femoral is secured last, for as long as the assistant retains his hold, hemorrhage from it is not to be-dreaded. Thus, when both surgeon and assistants are quick and cool, the operation may be completed with the loss of much less blood than might be expected."

A few years after this treatise was published, Liston wrote a letter describing his success with the use of inhaled ether in this same operation—amputation of the thigh. His success with the new anaesthetic drug announced to the world only a short time previously, is now a matter of history and marks a milestone in the advancement of medical practice.

To the editor of "Lancet" Liston wrote these words on December 21st, 1846.

My Dear Sir,

I tried the ether inhalation today in a case of amputation of the thigh, and in another requiring evulsion of both sides of the great toe-nail, one of the most painful operations in surgery, and with the most perfect and satisfactory results.

It is a very great matter to be able thus to destroy sensibility to such an extent, and without, apparently, any bad results. It is a fine thing for operating surgeons, and I thank you most sincerely for the early information you were so kind as to give me of it.

Yours faithfully,
Robert Liston.

Listons modest appraisal of the new anaesthetic agent was out of all proportion to the tremendous impact it was to have in the field of surgery in years to come, but it was typical of the man and his approach—short, concise and containing only the necessary details.

For some time after his historic operation Liston continued to practice his bold type of surgery. He is credited with having written an excellent monograph on inquinal and femoral hernia which was published in the Edinburgh Medical and Surgical Journal. He also devised a special laryngeal mirror and a shoe for club foot; devices for reducing dislocations and for cutting for stone; plastic operations on the nose and excision of the upper jaw.

Robert Liston died in 1847 from a ruptured aneurysm of the arch of the aorta, having complained of constriction in the larynx and difficulty in swallowing.

D. A. Dellandrea, B.Sc. 6T6

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Clinical Pathological Conference

Mr. M.B. age 39 yrs. Admitted N.M.S.H. Dec. 15, 1964, Died Jan. 8, 1965.

History of Present Illness

Patient was a 39 year old car mechanic who was apparently well until 6-7 weeks ago when he developed flu-like symptoms and subsequently started having diarrhea, 6-7 movements per day associated with crampy abdominal pain in the lower portion of his abdomen, before and sometimes after the bowel movement. Stool was watery, foul-smelling and brownish. His physician gave him pills which were successful in controlling the diarrhea in 2-3 days.

About the 10th day of his illness he felt weak and developed swelling of his legs and genitalia. He was admitted to Peel Memorial Hospital because of this. At this time his stools were soft but essentially normal, 2 per day. No evidence of blood since then. Since discharge from Peel Hospital he has tired easily. No history of dizziness, tinnitus, headaches or visual changes.

5 days prior to admission to this hospital he again developed diarrhea which lasted for 2 days. Since then stool has been well formed with neither blood, pus nor mucus. Appetite has been excellent throughout, but he has continued to lose weight, 25 lbs. in 2 mos.

No history of dietary intolerance, anorexia, exposure to toxins, fumes, metals or addictions of any kind. No dyspnea, cyanosis, cough or hemoptysis. No cardiac or urinary symptoms.

At age 30 he started getting abdominal discomfort, especially after food. His doctor told him he had a peptic ulcer but no X-ray was taken. He was given pills and a diet which he took for 2 years.

2 years ago he had diarrhea similar to the present episode. This lasted only 4-5 days and then cleared.

Physical Examination

Well developed but emaciated; pale and ill-looking; Wt. 131 lbs; B.P. 100/75; pulse 80/min; resp. 20/min; temp. 98.4°F. Pitting edema over feet, legs and scrotum. Skin dry, thin and scaly over lower extremities; suggestively pigmented over the back of the neck and forehead. Nails—pale and flattened; conjunctive pale; sclera clear; thyroid not palpable; lymph nodes not palpable. *G.I. System:* Abdomen distended, tense and tympanitic with striae. No shifting dullness or fluid thrill; no superficial venous engorgement; liver palpable one finger-breadth below costal margin, not tender; speen not palpable; no other masses palpable; no definite tenderness; external hemorrhoids present. *C.N.S. System:* paralysis of right lateral rectus mucle of the eye, no other neurological signs. *Respiratory System:* funnel-shaped chest, poor expansion. *Cardio-vascular System:* not remarkable. *U.G. System:* kidneys not palpable; prostate not remarkable. *Sigmoidoscopy:* No pathology in rectum or sigmoid, no ulceration or polyps.

Radiological Investigations

Chest X-ray: normal. *Upper G.I. tract:* esophagus, stomach normal. Slight deformity of duodenal cap but no definite ulceration. Some mucosal thickening in 2nd portion of duodenum. Just distal to mid-ileum, a few loops of ileum show an alternating narrowing and dilatation, loss of normal mucosal pattern with thickened bowel wall. Separation of bowel loops in this area suggest thickened mesentery. Proximal to this area, the bowel loops are somewhat edematous. *Barium enema:* normal. *Skeletal survey:* spina bifida lower end of sacrum. No other abnormalities.

Laboratory Tests

Stool: microscopy-fat globules present. Culture—no pathogens isolated. Occult blood—neg. to trace on two occasions. *Urinalysis:* Sp.Gr. 1022; sugar and protein—neg. Microscopy—normal. *Hematology:* Hgb. 11.4 gms%; R.B.C. 3.9; W.B.C. 4,000; ESR 30. Smear: RBC—slight anisocytosis; slight poikilocytosis; some polychromasia. Differential: Neutrophils 50, basophils 1, stab forms 41, lymphs 6, monocytes 2. Bleeding and clotting times normal; prothrombin time—18.5 sec. (control 14). Bone Marrow: essentially normal marrow, slight reactive plasmocytosis. *Biochemistry:* Sugar 90 mg%; BUN 12 mg%; CO_2 29 mEq/L; C1 103; Na 138; K 3.2 mEq/L. Ca 8.4mg%; Phosphate 3.1 mg%. Serum protein 3.42 gm%; Alb- 1.62; Glob- 1.8; AG ratio .9. SGOT 44 units; SGPT 36 units; Alk Phos. 19.6 units. Triosorb Resin uptake 34.6% (Normal 25-35%). Radioactive fat absorption test—colon excretion 16.7% (normal below 3%).

Course in Hospital

Patient was commenced on ordinary diet and later changed to high protein, low residue diet with multiple vitamin supplements. His general condition did not seem to improve very much and he continued to be uncomfortable. He remained afebrile. On Dec. 23rd pulse rose to 120 and remained above 105. At 7:00 a.m. on January 8th, he complained of feeling weak. His B.P. was 86/58; pulse 104. He was dyspneic, perspiring and very pale. At 7:15 respirations were labored; patient

was cold and clammy; placed on oxygen; B.P. unobtainable. At 7:30 respirations and heart ceased.

DIFFERENTIAL DIAGNOSIS

Dr. L. J. Cole*

The presenting symptoms at the onset were of a relatively young man with fever, diarrhea and lower abdominal cramps. At this point one thinks of an acute enteritis or enterocolitis resulting from infection with an enteric virus or some bacterial infection such as Salmonella. However there is no history of personal contact with such an infection. We then read that his stools became foul smelling. This might suggest that the diarrhea was not so simple, but rather associated with purulent discharge, the evaculation of an abscess or the sloughing of necrotic tissue from intestinal ulceration. The diarrhea responded to symptomatic therapy and recurred, associated with prolonged systemic upset forecasting a more serious situation. In any case diarrhea which lasts over 3 days merits very thorough investigation.

He suffered from weakness and developed edema of the legs and scrotum. These are unusual sequelae in a case of diarrhea of only ten days duration. The possibilities include some type of deep venous thrombosis or thrombophlebitis, associated for example with ulcerative colitis or some diffuse vasculitis, but there are no findings mentioned to confirm these suspicions. The question of lymphatic obstruction associated with inflammatory or neoplastic disease in the intestine or mesenteric nodes must also be considered. Edema associated with hepatic disease or portal hypertension is another possibility but there are no stigmata of liver disease in the protocol. Finally, edema resulting from hypoproteinemia associated with loss of protein from the gut, or a nephrotic syndrome are to be considered.

He sustained a weight loss of 25 pounds despite a good appetite and the recorded massive edema. This again indicates some serious debilitating disease possibly some form of mal-absorption syndrome with excessive loss of fat or protein in the feces. It is noteworthy that the diarrhea as recorded was never severe.

Nine years before his final illness, he noted abdominal discomfort, the nature of which is not detailed. He apparently was not investigated although he was told to follow a diet and take medicine. Two years ago transient diarrhea was noted similar to his present episode, suggesting that his illness might be of much longer duration and characterized by remissions and relapses. This consideration may be important in the final diagnosis of the patient.

The salient findings on examination indicates the absence of sub-standard development which might be expected in chronic cardiac or celiac disease. He does have evident weight loss substantiating the history. There are no indications of systemic venous congestion or portal hypertension. The edema is as previously described, apparently without ascites at this time. There is no lymphadenopathy. His pallor may well be the result of both anemia and edema. The cutaneous changes described are non-specific and may be encountered with chronic enteritis, chronic ulcerative colitis, with liver disease, steatorrhea and so on. No peritoneal signs were elicited. The normal findings on sigmoidoscopy exclude neoplasm in the area examined such as carcinoma or multiple polyposis. The normal sigmoidoscopy excludes universal but does not exclude segmental ulcerative colitis or ileocolitis.

Reviewing the laboratory findings, the stools were negative on culture excluding a specific bacterial infection as a primary cause. Feces were negative for occult blood on two occasions; however this does not exclude ulcerative disease of the bowel. Fat globules are noted in the stool. A small amount of fat in the stools may be normal, whereas a lot of fat may be due to mal-absorption or pancreatic insufficiency.

The urinalysis indicates normal renal function without objective evidence of kidney disease. Hematologically we have a moderate anaemia with some young red cells, a shift to the left in the neutrophils despite a normal total leukocyte count and an active bone marrow. The slight plasmocytosis is a non-specific finding which may be encountered in a number of situations. The slight prolongation of prothrombin time may be related to a mal absorption, impaired liver function, disturbed protein metabolism or a combination of factors in this patient.

His serum proteins show a marked hypoproteinemia and hypoalbuminemia. The liver profile is non-specific pointing to hepatocellular impairment. It could be related to previously administered drugs, or less likely the residual of hepatic infection years ago. Most likely it is related to his underlying disease since both regional enteritis and ulcerative colitis may be associated with hepatic involvement and particularly in ulcerative colitis it may actually progress to biliary cirrhosis. Malabsorption is indicated by the reduced fat absortion and steatorrhea. Unfortunately no tests were recorded (eg. fecal analysis following IV injection of radio-iodinated serum albumin) to demonstrate excessive protein loss into the gastro intestinal tract. However, in the clinical setting presented, it is reasonable to attribute the hypoproteinemia and its sequelae to excessive loss of protein in the gut. We might now take a look at his X-rays.

Dr. B. J. Shapiro

The chest X-ray is normal. The barium filled stomach is normal and there is no evidence of giant gastric rugae which would be associated with a protein losing gastritis such as Menetrier's syndrome.

*Senior Attending Physician, Senior Gastroenterologist, New Mount Sinai Hospital, Toronto; Assistant Professor in Medicine, Toronto Medical School.

The essential radiological findings are the possibility of a pre-existing duodenal ulcer, mucosal abnormalities in the duodenum and the ileum and the indications of disease in the mesentery.

DR. L. J. COLE

The clinical findings point to intestinal disease likely with protein loss into the gut. Protein lost through the gastro-intestinal tract may orignate from ingested food, from secretions, from blood, pus and from tissues sloughed from the intestinal wall. Normally the protein content of the alimentary secretions is approximately 35 gm in 24 hours; but the loss of protein in the stool is negligible, so that these secreted proteins and their digestive products are almost completely absorbed. Normally 100 cc's of blood contain 15 gm of hemoglobin and 7 gm serum proteins. Alimentary tissue is 30% solid of which 2/3rds is protein, so that a loss of 100 gm of alimentary tissues removes 20 gm of protein from the blood. It becomes evident that bleeding and ulcerative gastrointestinal lesions may be associated with considerable protein loss.

Protein losing gastroenteropathy is recorded in many situations: *Menetrier's disease* which is characterized by giant rugae in the stomach and bowel, which have not been demonstrated in this case. *Intestinal lymphangiectasia,* in this case there is no family history and the radiological findings here suggest mucosal destruction rather than mucosal oedema. *Celiac disease* or *adult primary mal-absorption syndrome* may be associated with an excessive leakage of plasma proteins. However there is a lack of the usual radiological findings but rather positive findings of mural intestinal disease. *Gastric carcinoma*—can be excluded. *Intestinal lymphoma,* the radiological features do not suggest this, but it has been confused with regional enteritis. *Prolonged Salmonella infection of the bowel* has been reported to cause protein losing enteropathy. Despite the acute febrile onset of the present illness, the negative bacteriological study and the subsequent clinical course exclude this diagnosis. The syndrome has been reported with constrictive pericarditis, nephrotic syndrome and Whipple's disease, but these can be excluded here. *Non-specific granulomatous disease of the small bowel and messentery* is essentially a tissue diagnosis and cannot be excluded on the basis of the symptoms and findings presented. *Ulcerative colitis* cannot be diagnosed here in the absence of positive findings either on sigmoidoscopy or radiological investigation. *Radiation enteritis* need not be considered in this case. *Chronic regional enteritis* best fits the clinical,, laboratory and radiological findings. This man probably suffeied primarily from *chronic regional enteritis* and he likely had extensive involvement of his mesenteric lymphatics and possibly the duodenum. The liver may show non-specific chronic hepatitis with pericholangitis or granulomatous lesions such as seen in Crohn's disease.

Finally, in determining the cause of his sudden demise, it is doubtful that it was due to an exsangulinating hemorrhage, bowel perforation or a sudden cardiac or cerebro-vascular accident. The prolonged bed rest, massive edema, the dehydration associated with diuretics and purgation, may all have pre-disposed to phlebothrombosis and terminal massive pulmonary embolism. Phlebitis with intestinal inflammation, would be a much less likely source of emboli.

CLINICAL DIAGNOSIS

(a) Protein losing enteropathy due to Crohn's Disease (Regional Ileitis).

(b) Sudden death due to pulmonary embolism? due to leg vein thrombosis.

(c) Mild cholangitis.

PATHOLOGICAL DISCUSSION

DR. H. T. G. STRAWBRIDGE

Massive pulmonary embolism was the cause of the sudden death. The major portion of the embolus was jammed into the main right pulmonary artery. The leg veins were not examined but none of the abdominal or pelvic veins had any thrombi so it is presumed that the embolus did in fact originate from the leg veins. Otherwise the lungs were essentially normal.

The other findings were confined to the gastro-intestinal tract. The stomach was normal. There was no evidence of ulceration or scarring in the duodenal cap, but the duodenal mucosa was congested. Histologically there was a mild but definite non-specific duodenitis. The jejunum showed slight congestion of the mucosa but was of normal thickness and appearance in general as was the upper part of the ileum. Commencing 170 cms. from the ileo-cecal valve and extending for a distance of 100 cm. the serosa of the ileum was dark and congested. In this segment the bowel wall felt thicker than usual and on section there was indeed slight thickening zones where the normal folds of mucosa were absent. It was difficult to assess how much if any ulceration was actually present and certainly there was no gross evidence of fibrosis. The distal 70 cms. of ileum were essentially normal as was the colon.

The mesentery of the small bowel was only suggestively edematous but the lymph nodes therein were nearly all enlarged and readily seen; all nodes were discrete.

The liver weighed 1830 gms. and was paler than usual, somewhat soft in consistency. The gall-bladder, bile ducts and pancreas were normal.

Histologically there was a complete loss of the villi and virtually all the epithelium leaving an intensely

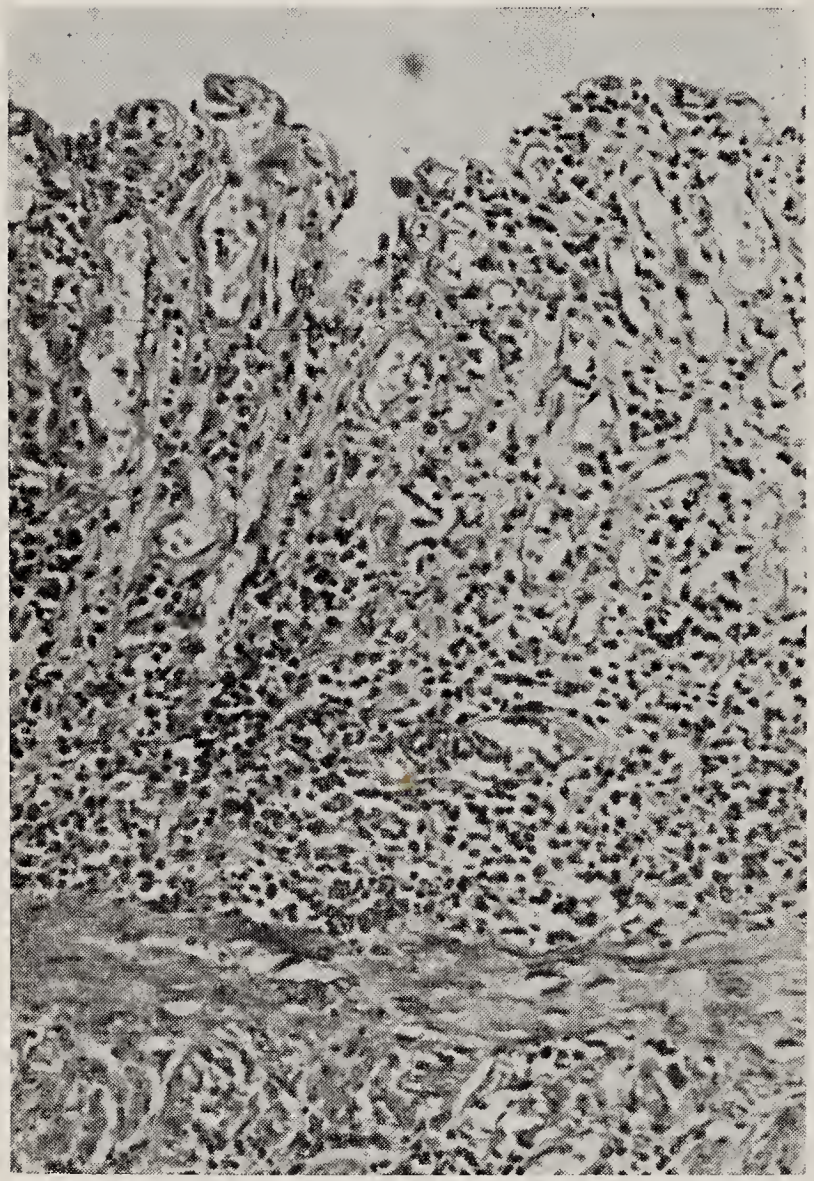

Fig. 1. Mucosa of ileum showing loss of epithelium, marked, predominantly plasmacytic, inflammatory infiltrate and prominent capillaries in lamina propria. H & E x 160.

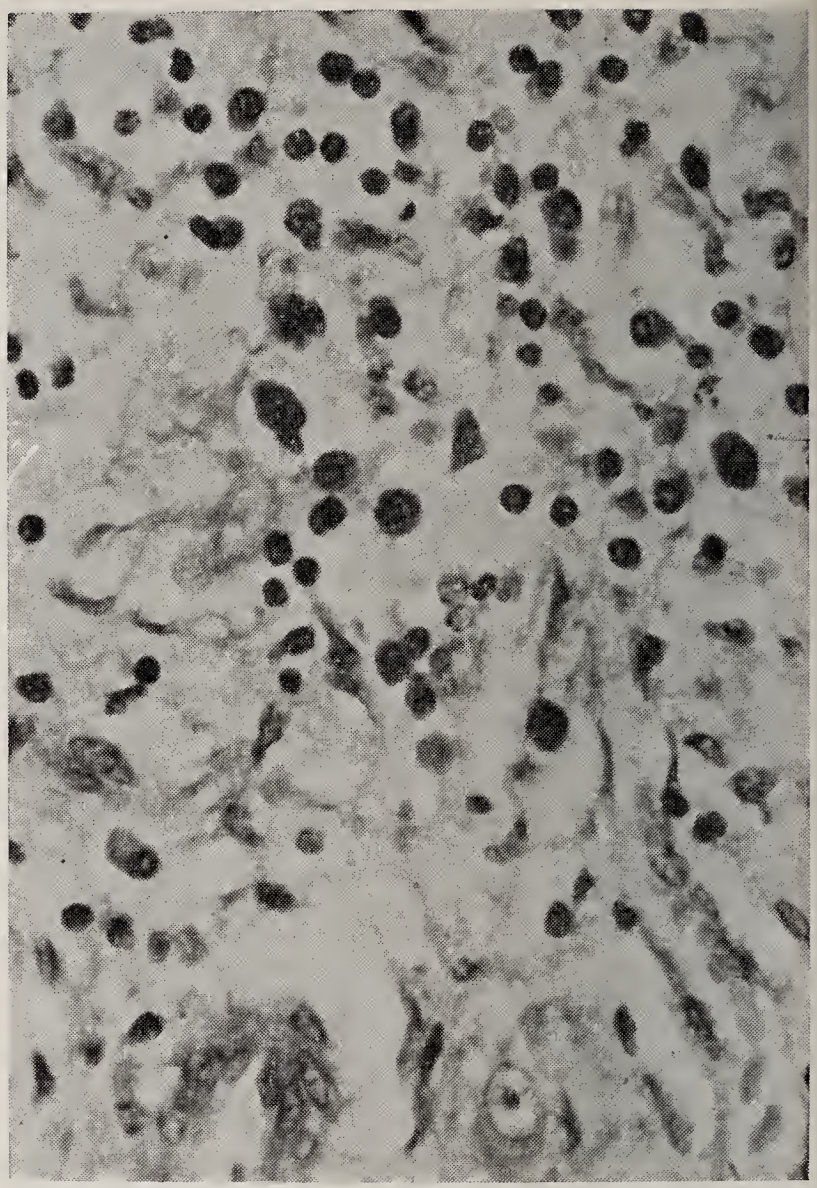

Fig. 2. Submucosa of ileum. Oedema and plasma cell infiltrate. H & E x 500.

inflammed lamina propria in which there was a pronounced plasma cell infiltration along a few eosinophiles. Lymphocytes and histiocytes were relatively infrequent (Fig. 1). There was marked dilatation of the capillary bed and in places it appeared that new capillaries might be performing in view of the plump endothelium of these vessels. The intense vascularity and absence of epithelium affords a ready explanation for the protein and fluid loss through such a surface. The submucosa showed a similar picture with marked edema (this accounted for a major portion of the thickening of the bowel wall), dilatation of the vessels, and plasma cell and eosiniphilic infiltration (Fig. 2). This extended throughout the muscularis but was more patchy and relatively mild; there was as yet no fibrosis.

Anatomically this lesion is certainly a regional enteritis and there is no evidence of the crypt abscesses or intense polymorphonuclear infiltrate that is found with ulcerative colitis when it occurs in the ileum. Although no granulomas were found, the general distribution and character of the infiltrate appears to fall within the spectrum which can be labelled Crohn's Disease.

Sections of the lymph nodes showed merely a nonspecfic reactive hyperplasia with marked plasmocytic proliferation along with some eosinophiles. No granulomas were present.

The liver showed a moderate degree of fatty change with in many places quite large fatty vacuoles in the cells, with a tendency to periportal distribution. Some of the portal tracts showed quite well marked cholangitis with predominantly lymphocytic and plasma cell infiltrate and a few proliferated bile ductules. It is presumed that the fatty change can be explained on the basis of the nutritional upset in relation to the intestinal condition, and the cholangitis regarded as an ascending phenomenon.

PATHOLOGICAL DIAGNOSIS

(a) Crohn's Disease (Regional Ileitis) of distal but not terminal ileum.

(b) Massive pulmonary embolism? due to leg vein thrombosis.

(c) Fatty change in the liver.

(d) Mild cholangitis.

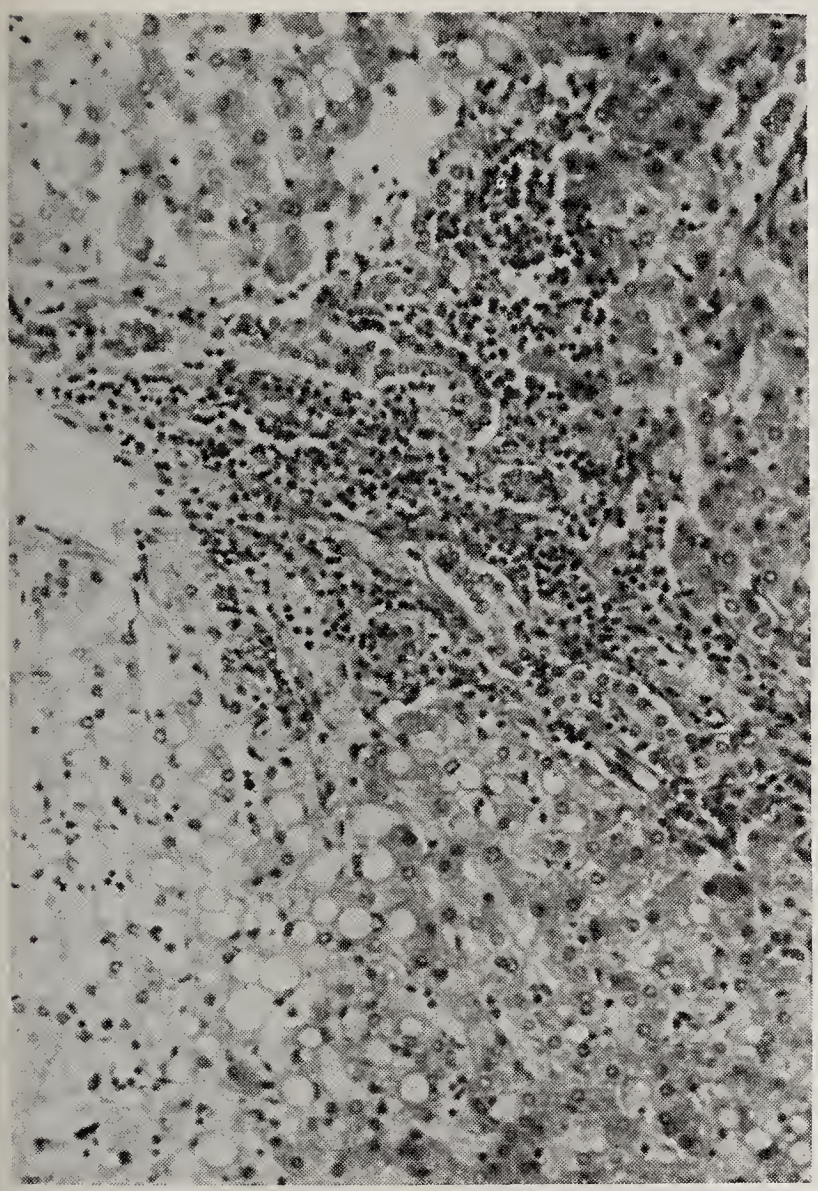

Fig. 3. Mild cholangitis and fatty change in liver. H & E x 100.

DISCUSSION

Dr. D. Bohnen

The protein and fat losing qualities of enteropathies, particularly regional enteritis tends to be minimized. Fortunately, it does not occur in all of them but occurs particularly in those that have an obstructive element to them.

In this case, the conservative approach to management must be respected. First of all he was a serious nutritional problem and this had to be corrected to some extent before anything definitive of a surgical nature could be entertained, and secondly this was not a typical terminal enteritis. The fact that the disease was regional in the ileum certainly suggested the possibility that this might be segmental, that there might be more than one segment which was not recognized radiologically; in these cases one tends to be conservative. Had this patient been operated on, chances are a reasonably good result might have been attained but these are the very patients who are more prone to develop recurrences of their disease.

Dr. Houpt:

I wonder if you could give us any information Dr. Cole, on any new ideas as to the relationship between the small and large bowel lesions with the auto-immune disease?

Dr. L. J. Cole

A good deal has been written about the auto-immune mechanism in inflammatory diseases of the large and small bowel, particularly non-specific ulcerative colitis and Crohn's disease. Although clinical and laboratory features seem to implicate hypersensitivity influences, and the colon at least is capable of immunological reactions, attempts to produce immune colitis have been inconclusive. Necrotizing enteritis and colitis have been reported in diseases currently associated with hypersensitivity, particularly D.L.E. and polyarteritis. Despite the clinical and experimental studies, there is no definite indication as to whether the findings are the cause or the result of the disease. They do not show the histological granulomas usually associated with classical Crohn's disease; and they have not as yet been reported to be associated with protein losing enteropathy.

ACKNOWLEDGEMENT

Most sincere thanks to Dr. Strawbridge, senior pathologist at New Mount Sinai Hospital, whose efforts made this presentation possible.

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Recent Advances

EEG: Sensory Evoked Response

The sensory evoked response is a series of definite electrical potential changes that may be recorded at the cerebral cortex or other sensory centres of the brain following peripheral sensory stimulation. These sensory responses, however, are usually of an amplitude far less than that of the normal brain activity and therefore are difficult to observe in electroencephalographic recordings. Electronic averaging techniques may be used to separate the evoked potentials from the background electrical activity of the brain. A certain sensory stimulus is repeatedly presented and the electroencephalographic records immediately following each stimulus are averaged. The normal electrical activity of the cortex may be considered as random and during repetition will effectively average to zero leaving the sensory evoked response, which being "time-locked" to the stimulus remains constant.

The sensory evoked response may be considered in four forms:

1. *Primary Evoked Response*—a potential change of short duration and latency that may be recorded at the exposed specific sensory cortex and that is probably a result of passage of impulses along specific or lemniscal sensory pathways.

2. *"Secondary" Evoked Response*—a much longer lasting response that may be recorded rather diffusely over the frontal cortex. The wide distribution of the response probably explains why it may be recorded fairly easily at the human scalp. This secondary response is perhaps characterized by its variability: it changes markedly with the attentiveness of the subject and with the intensity or significance of the stimulus. Stimuli of different sensory modalities give responses similar but distinctly separate—the presentation of two different stimuli together produces a response equivalent to the algebraic sum of the individual responses. Most theories agree that the response represents "awareness" as conveyed by the thalamic reticular system, including the dorso median nucleus, and quite probably "specific sensory information" as conveyed by cortical association fibres.

3. *Contingent Negative Variation*—a later negative wave occurring after the secondary response probably mediated in the midbrain reticular system. It is especially prominent if the evoking stimulus is a signal for later motor action; it may therefore demonstrate cortical "priming" or "preparedness".

4. *Rhythmic After Discharge*—there may occur after a stimulus, especially visual, a diffusely recorded rhythmic wave-form bearing a striking resemblance to the cortical alpha rhythm.

Cortical evoked response research is twofold—on the one hand to determine the exact nature of the recorded response; on the other to use the response as a clinical or neurophysiological investigational aid. The evoked response has already been used in many varied fields.

1. *Congenital Deafness* In order that a congenitally deaf child may learn to talk properly, his deafness must be recognized before the child is a year old so that hearing aids may be provided. Before the use of the sensory evoked response the clinical recognition of deafness in the infant was extremely difficult and the evaluation of hearing-aid effectiveness even more so. With the evoked response, however, a rapid evaluation of the infant's auditory acuity at any intensity or frequency of sound is possible. It is hoped that it may soon be possible to screen-test all new born infants for congenital deafness. Congenital deficiencies of other senses may, of course, be similarly recognized.

2. *Psychology of Learning* The sensory evoked response together with other electroencephalographic data aid in presenting a neurophysiological explanation of learning. Having repeatedly presented a subject with a set of two stimuli separated by a time interval, the first alone may be presented—a definite sensory evoked response will be recorded at the time when the second stimulus should have been. This, then, represents a neurophysiological demonstration of "pattern retention", such memory probably being in the reticular system. During classical Pavlovian conditioning when the reflex is being learned a distinct contingent negative variation follows the conditioned stimulus. Once the reflex is learned, however, this negative variation is no longer present—it is as if the conditioned stimulus is "broadcast" until a final simple and subcortical pathway is opened (by means of this general broadcast) to deal with the stimulus.

3. *Psychiatry* The sensory evoked response is of course an excellent means of studying perception. It is probable that hysterical sensory symptoms may be differentiated from definite neurological deficiencies by the presence or absence of the sensory evoked response. There are definite changes in the auditory evoked response of a subject in delirium tremens experiencing auditory hallucinations. Thus it may be quite possible to use the sensory evoked response to differentiate between toxic and functional hallucinatory states. Recent research has shown that the rhythmic after-discharge

was not present in delirium, sleep, chronic brain damage or barbiturate narcosis and has suggested that this discharge may represent in some way the psychiatric concept of an "intact and functioning sensorium".

In one study the "recovery function" of the human visual cortex was measured by determining the effect of one light flash following almost immediately upon a previous light flash. The ability of the cortex to respond to this second stimulus was decreased in a wide variety of psychiatric patients. This points to a possible deficiency of post-synaptic neuronal recovery following stimulation, perhaps chemical in nature.

The sensory evoked response will undoubtedly become a very effective diagnostic tool; one may presume that in a few years the determination of sensory evoked responses will be almost a routine part of electroencaphalographic examination.

T. Picton 6T7

ACKNOWLEDGEMENT

Sincere thanks to Dr. J. W. Scott, Professor of Physiology, University of Toronto.

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Abstract

The Pineal Gland

Richard J. Wurtman, Julius Axelrod: Scientific Am., Vol. 213, No. 1, July 1965, pp. 50 - 60.

This article discusses recent evidence that the pineal gland is a "biological clock" converting cyclic nervous activity generated by light in the environment into hormonal information, i.e., that the gland is a neuroendocrine transducer.

For more than fifty years it has been known that pineal tumours are often associated with precocious or retarded sexual development, chiefly in boys. The tumours associated with early sexual development were found to be tumours of supporting tissue or teratonias. The ones associated with retarded development were mostly true pineal tumours. It was postulated that the pineal exerted an inhibiting influence on the gonads.

The mammalian pineal originates in the embryonic brain but subsequently loses all nervous connection to it. It is, however, extensively penetrated by sympathetic nerves. In structure, it is analogous to the adrenal medulla.

A substance, melatonin, which blanches the skin of tadpoles, was first isolated from cow pineals. The substance appears to be metabolized from 5-hydroxytryptophan in the pineal. In addition to skin effects, melatonin, administered to female rats in small doses, slowed the estrus cycle and caused the ovaries to lose weight. Radioactive labelled melatonin was found to be taken up by the brain, pituitary, ovaries and vagina of injected rats.

Other workers have shown that, in rats, continuous environmental illumination was associated with a decrease in pineal weight. The authors found that melatonin synthesis in animals in constant light was about one fifth that of animals in continuous darkness. They established that light information was transmitted to the pineal via the eyes, superior cervical sympathetic ganglia and sympathetic nerves. Blinding the rats or removing the ganglia abolished the response to light.

Lighting cycles are important in the regulation of several types of endocrine function: the coming of spring, with an increase in sunlight, triggers breeding cycles in many birds and mammals. Circadian (about one day) rhythms in adrenal steroids are thought to be governed by diurnal lighting changes. The rate-limiting enzyme in the production of melatonin was found to fluctuate with diurnal light levels, being highest about midnight. This fluctuation was rapidly extinguished by blinding the rats or placing them in continuous darkness. Other investigators discovered an inverse variation in pineal serotonin levels (peak at noon). This cycle was not as rapidly extinguished by darkness or blinding.

Thus the pineal gland contains at least two distinct biological clocks infuenced by changes in environmental lighting. M.S.

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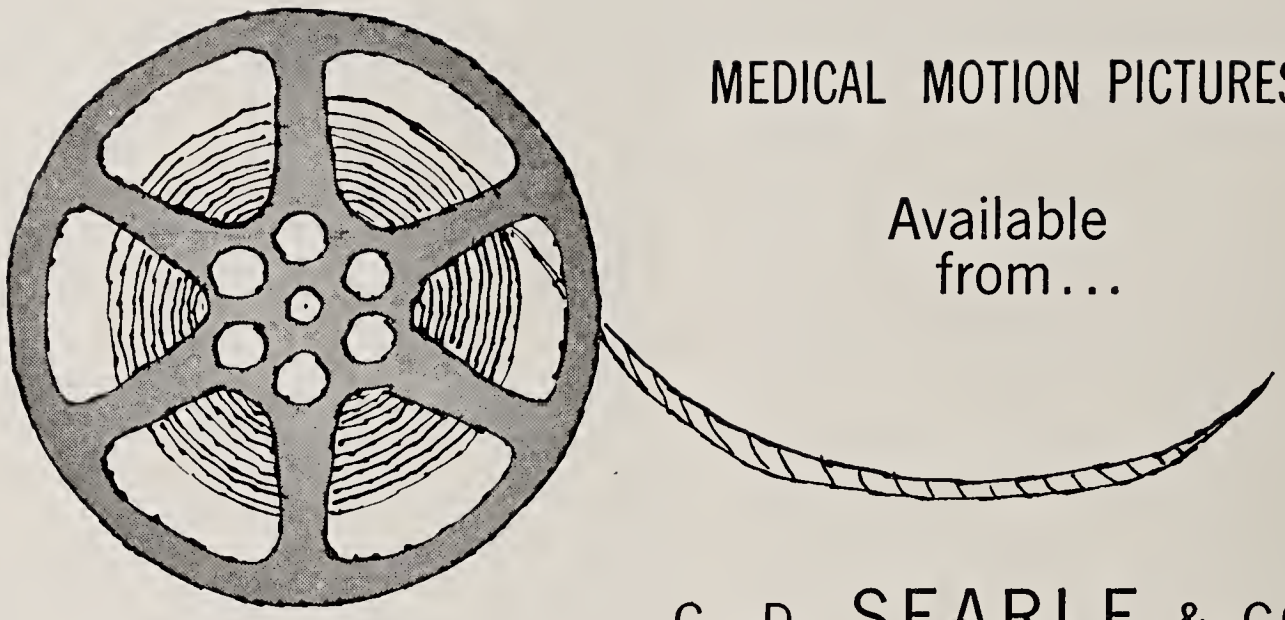

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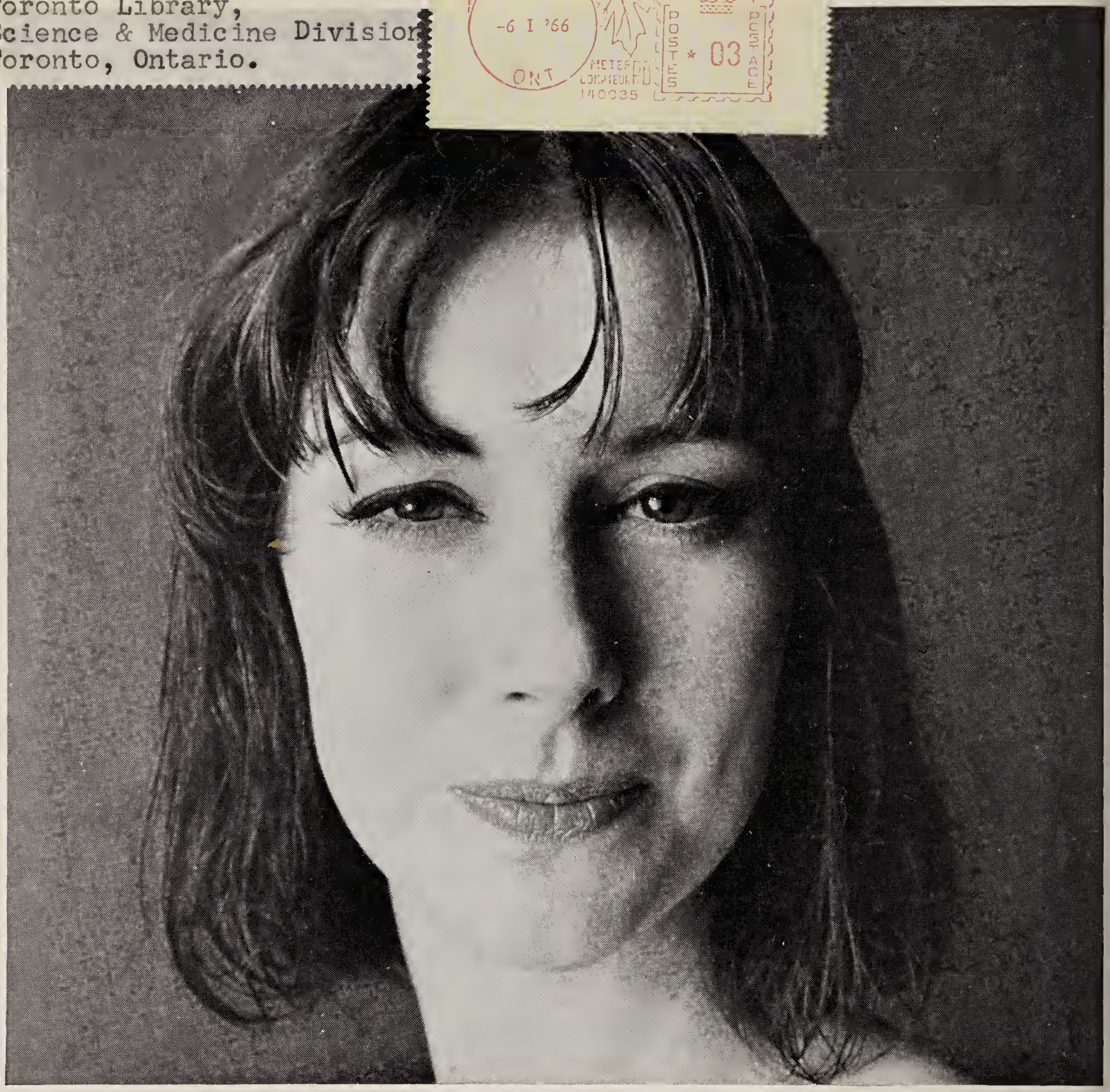

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